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Review Article

Trace elements in health and disease

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ABSTRACT

Trace elements are micronutrients that cannot be synthesized by human cells. The origin of all elements represented in the periodic table of elements at the present time is probably in the dying stars and supernovas billions of years ago by thermonuclear fusion reactions. Essential trace elements play vital roles in the maintenance of human health. During the last few decades, we have seen an explosion of new knowledge concerning the role of trace elements such as iron, zinc, copper, iodine and selenium in human health and disease. Iron deficiency anaemia, growth retardation and hypogonadism due to zinc deficiency, Wilson's disease due to inherited copper toxicity, Keshan disease in China due to selenium deficiency causing cardiomyopathy are good examples illustrating the impact of a few trace element deficiencies. In terms of people afflicted with anaemia due to iron deficiency, it is second only to protein-calorie malnutrition. Recent knowledge regarding hepcidin and ferroprotein has provided greater insights in the mechanism of haemostasis and iron storage disorders. Several other pathological conditions in animals including man are implied to be associated with the deficient intake of trace elements such as zinc and selenium. Zinc is now known to be essential for DNA synthesis, cell division and growth. Currently, we know that nearly 300 enzymes and more than 2000 transcription factors in human are zinc dependent. Although malnutrition and starvation are restricted to certain poverty-stricken areas of our planet, it has become increasingly evident that a marginal/subclinical deficiency of trace elements such as iron, zinc and selenium is common even in affluent countries. The dietary intake of several trace elements investigated by the present author in Sweden is within current recommended intake levels. During the last few decades, the implications of toxic metals such as lead in the environment became a very important health issue in industrial as well as developing countries. Lead alone or in combination with other metals was widely used from historical times. Lead in cosmetics is still used in some parts of the world. Lead is a toxic metal that affects every biological system in the human body. A short summary on the effect of lead on various systems of the body will be given in this review.

KEY WORDS: copper, iron, lead, selenium, zinc

INTRODUCTION

The search for facts and figures concerned with the origin of our universe and life on earth that can link different types of knowledge is as old as humanity itself. The modern story of the origin of our universe and life on earth is less stable, more turbulent and much larger than the worlds of many traditional origin stories due to the latest advancements in science and technology. According to modern cosmologists, astronomers and physicists, everything started after the big bang, 13.82 billion years ago. The crucial parts of the big bang story emerged during the early parts of the 1960s, when scientists could detect cosmic microwave background radiation everywhere in the universe. This energy is left over from the big bang and it is present everywhere in the universe. The first and lightest element formed immediately after the big bang by nucleosynthesis was hydrogen, followed by helium. These elements were followed by trace amounts of lithium and beryllium. The nuclear fusion of other elements such as carbon and oxygen in the stars resulted in the synthesis of elements like magnesium, silicon and iron. When a star explodes finally in a supernova, it will synthesize most of the remaining elements found in the periodic table of elements and blast them into space. Almost all other elements found in nature at present is thought to be created by various natural methods of nuclear fusion. Our sun and solar system were formed about

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Table 1: The origin of chemical elements

Events	Approximate date	Elements formed
Big Bang	13.82 billion years ago	Hydrogen, helium, lithium, beryllium
First Stars	13.2 billion years ago	Carbon, oxygen and other elements including Iron
Dying Stars	13.2-4.5 billion years ago	All elements in the periodic table up to Uranium (92)
Our Solar system	4.5 billion years ago	All naturally occurring elements
First sign of Life on Earth	3.8 billion years ago	Most elements as above
Emergence of Homo Sapiens	200,000 years ago	All elements as above

4.5 billion years ago and the earliest known life on earth was estimated to be formed about 3.8 billion years ago[1-3].

The discovery and use of some of the elements such as sulphur, copper and gold began with primitive human societies. Much of the current understanding of chemical elements developed from the work of a Russian chemist, Dmitri Mendeleev, who published the first recognizable periodic table in 1869[4]. This table organizes the chemical elements by increasing atomic number into rows in which the columns share recurring physical and chemical properties. Towards the end of 2016, the International Union of Pure and Applied Chemistry had recognized the occurrence of a total of 118 chemical elements in our planet. The first 92 (94) occur naturally on earth and the remaining 24 are synthetic elements produced in nuclear reactions like the nucleosynthesis in the early stars 13.2 billion years ago. Except for a few radionuclides, most of the chemical elements are available industrially in small or large quantities at present. It is likely that the number of the elements found in a modern periodic table of elements is likely to increase in the future with the advancement of science and technology.

The planet we live in is one of the most extraordinary places in the known universe. In all the shining abundance of living and dead celestial objects in the universe, the earth is the only place that harbours life as we know at the present time. When the earth was formed around 4.5 billion years ago, it was a sterile rock with most of the chemical elements present in various layers. There are many conflicting theories about the origin of life on earth. At the same time, most scientists agree that proteins, genes and cell membrane are the basic constituents of all life forms. All these components are formed from the bulk of chemical elements shown in the periodic table. Most life on our planet is microscopic and single-celled. They probably evolved during the first billion years of our planet's existence. As time passed, cyanobacteria started photosynthesis to extract energy from their environment and produced oxygen. By doing this about 2.4 billion years ago, they fundamentally changed the planet and created conditions for more complex life-forms to evolve. When oxygen first started accumulating in the air, it plunged our planet into a crisis. The rise of oxygen in the atmosphere wiped out a greater proportion of life than in any other mass extinction. However, the very property that makes oxygen so dangerous, its high reactivity, also makes it a rich source of energy. Photosynthesis harvests sun's energy. Plants use this energy to make food by building chains of carbon from carbon dioxide and ultimately yielding sugars. This can be used as an energy source to make more complex molecules, from proteins to DNA. This review will try to describe the nature and health effects of some of the most important chemical elements. The events that resulted in the formation of the periodic table is shown in Table 1.

LITERATURE REVIEW

The classification of chemical elements

As mentioned earlier, the current periodic table of elements contain 92 naturally occurring elements out of the 118 known elements. Hydrogen and oxygen (water) alone constitutes 60-65% of an adult human body weighing 70 kg. Rapid advances in analytical technology and sophisticated instrumentation introduced during the last few decades have not only helped to recognize the presence of most of the naturally occurring elements in living systems and their food chain but have also added a new dimension to our understanding concerning the role of elements in health and disease. Table 2 shows the classification of elements that are found in an adult human body.

Table 2: Early classification of chemical elements found in an adult human body

Traditional category	Elements
Major elements (bulk)	carbon, hydrogen, oxygen, nitrogen, sulphur, calcium, phosphorous, potassium, sodium, chlorine, magnesium
Minor elements (Trace)	iron, zinc, copper, manganese, nickel, cobalt, iodine, molybdenum, selenium, chromium, fluorine, silicon, tin, vanadium, arsenic, boron and others
Toxic elements	Arsenic, cadmium, lead, mercury and probably others

It is rather impossible to find a meaningful classification of the chemical elements or even to draw a completely satisfactory line of demarcation between the different categories of the elements. As mentioned earlier, one can detect the presence of most naturally occurring elements in many tissues of an adult human body employing the latest analytical technologies. Traditionally, the term "trace elements" is given to a group of chemical elements as shown in Table 2. The concentration of many of these elements in living tissues and circulating fluids are much lower than that of the bulk elements and as such they could not be quantified accurately until recent years and hence, they were termed as trace elements[4]. Recently, it has been suggested that the elements found in the human body and other biological materials should be classified as essential or non-essential when they are discussed in relation to health and disease. The number of chemical elements that are found to be of importance in health and disease is likely to increase in the future. Ultimately, we may be dealing with all the naturally occurring chemical elements in the periodic table. At least, such a trend for an expansion has been noted during the last few decades[5,6].

The clinical and nutritional importance of the so-called trace elements has grown rapidly during the last century due to better understanding of their biological functions. In deficiency states, most trace elements with major metabolic events create health problems in man and animals. Iron deficiency anaemia is a good example illustrating this. In terms of people afflicted, it is second only to protein-calorie malnutrition. Several other pathological conditions in man and animals are implied to be associated with deficiencies of trace elements. Although malnutrition and starvation are restricted to certain poverty-stricken areas of the globe, it has become increasingly evident that a sub-clinical deficiency of several trace elements including zinc, copper and selenium is common even in affluent countries[5,6]. Establishment of the optimum daily requirements and the determination of the actual daily intakes are important current problems of trace element nutrition. Further, the intake levels that produce either a sub-clinical deficiency or toxicity, especially in vulnerable groups, are still being discussed. Basic biochemical mechanisms by which certain trace elements such as copper, manganese and vanadium influences metabolism and causes clinical deficiency symptoms in man both primary and secondary, are not yet definitely and completely elucidated. In recent years, it has been found that the chemical structure of trace elements as found in food for human consumption and the interaction between each other and with other nutrients play important roles in their absorption and metabolism. Moreover, the importance of supplementation of food stuffs, from a public health point of view, and clinical interest in total parenteral nutrition are current issues of importance. The influence of certain trace elements such as zinc, copper, iron and selenium in the ethology and progression of certain malignancies and altered immunocompetence has become another important area of trace element research in recent years[7].

The purpose of this review is to provide the latest information concerning the role of a few trace elements in health disease. It is not possible to write about all the essential trace elements because of the vast literature available that relate to the essentiality and health effects of most of the trace elements. In this review, a more detailed information concerning the role of zinc, iron, copper, selenium and lead in human health and diseases will be provided. Most clinicians and researchers are familiar with the role of other trace elements such as molybdenum, vanadium, iodine, manganese and chromium. Only a brief description of these elements mentioned earlier, concerning their health effects will be provided in this review. The health effects of toxic metals like arsenic, cadmium, mercury and others are not covered in this review due to shortage of space. Since lead is an important toxic metal from an environmental and public health point of view, a brief summary of the health effects of this metal is included in this review. Important literature is available in the reference list provided in this article.

Iron

Traditionally, iron is one of the classical elements that belong to the group of essential trace elements. This element has been known to mankind from ancient times. The ancients believed that iron is of heavenly origin. The Greeks and Romans believed that iron was a gift from Mars. Iron is one of the most abundant elements in earth. It is a vital element in all living things. Around 1/3 of the mass of our planet is iron, which is the largest proportion of any element, followed closely by oxygen. In earth's crust, however, the metal is the fourth abundant followed by oxygen, silicon and aluminium. The iron rich core is at the centre of the planet. Iron exists in a wide range of oxidation states, with the ferrous/ ferric states being the most common biological forms. During the 19th and early 20th centuries, the importance of iron was closely linked with the treatment of chlorosis[8,9]. The presence of iron in tissues was first demonstrated in 1713 by Lenny and Geoffy[8,9]. In 1886, Zinoffsky estimated the iron content of horse haemoglobin[9]. Following this important discovery, attention was focused for many years on the role of iron in the formation of haemoglobin. In each cell of human and animal bodies, many vital reactions depend upon the

presence of iron, including DNA synthesis. In plants, it is involved in photosynthesis. Cytochromes are heme-proteins that facilitate electron transfer, apoptosis and metabolic detoxification[10,11].

An adult human body contains 4-5 g of iron, and more than half this amount is bound up in haemoglobin. Myoglobin and enzymes containing heme or non-heme constitutes 5-6% of total body iron. Almost a quarter of the total body iron is stored as ferritin and hemosiderin, mainly in the liver. Hepatocytes also produce hepcidin, which is a cysteine-rich peptide[11]. This peptide is the master regulator of iron metabolism. Once iron enters the hepatocyte, it is either stored as ferritin or exported at the basolateral membrane to the plasma of the splanchnic circulation by ferroprotein[12]. Membrane ferroprotein in turn is regulated by hepcidin[12]. The levels of hepcidin in the body is regulated by iron status, inflammation and expansion of erythroid precursors[13]. Recent knowledge regarding hepcidin and ferroproteins have provided greater insights into the mechanisms of iron homeostasis and about iron storage diseases. Increased iron stores are associated with several disorders including hemochromatosis, dysmetabolic iron overload syndrome and African dietary overload. In sub-Saharan African countries, iron overload is observed in 15% of the male population living in rural areas[14]. Dietary overload of iron may lead to fibrosis and cirrhosis of the liver. About the details of iron metabolism with reference to the latest findings on hepcidin and ferroproteins, the reader is advised to look in latest textbooks of haematology.

From a nutritional point of view, iron deficiency is one of the most important public health problems. In numbers of people affected, it is the leading factor that contributes to the global burden of anaemia. It is next to protein-calorie malnutrition and over 1.62 billion people are affected[15]. Iron deficiency can lead to mood changes such as irritability and depression, cause neurodevelopmental delay in children, precipitate heart failure, and cause restless legs syndrome[11,16]. Prussian blue staining of the macrophage iron in a bone marrow aspirate is one of the accepted tests for diagnosing iron deficiency anaemia[11,16]. There have been several proposals for and investigations of fortification programmes, particularly in developing countries, where the prevalence of iron deficiency anaemia is high. Strategies to fortify or enrich food consumed by susceptible population on the other hand have met considerable opposition from physicians and health authorities who consider the risk for iron overload overweighs the benefit of supplementation. A review some decades ago by Finch and Monsen showed that an increase in the dietary load of iron from 300-400 μmol (16-25 mg) did not result in an increase of the absorbed iron[17]. The efficacy of iron absorption is also facilitated by the presence of proteins and amino acids, which either stimulates acid secretion or by forming amino acid chelates of iron. Fortification of flour with iron may not be beneficial. In Sweden, 43% of the food iron in 1973, however, originated from fortification. In recent decades, fortification of milk and common salt with iron had considerable success in preventing iron deficiency anaemia[18,19].

Iron status is usually judged by measuring transferrin saturation, concentration of serum/plasma iron, red cell protoporphyrin and serum/plasma ferritin. Deviation of these parameters from the normal values, however, do not always indicate a change in iron status[18-22]. When all the above parameters are abnormal, iron metabolism is always deranged. Cook and others in 1976 investigated the iron status of a large population by measuring three of the above parameters and found that 63% of the subjects had anaemia[19]. Low levels of ferritin in serum (less than 10 ng/l] always indicate a very low body status. Iron deficiency anaemia is often defined according to the decrease in haemoglobin levels. Haemoglobin levels on the other hand, may not always explain symptoms because of the adaptation of oxygen transportation mediated through 2,3 diphosphoglycerate.

Studies by the present author and others in Sweden in vulnerable groups such as pensioners and pregnant women have indicated no sign of iron deficiency and there is no indication for iron supplementation. Whenever iron deficiency is suspected and before starting a supplementation program, it is important to look for any pathological conditions such as a serious bleeding, other than a pure nutritional deficiency. Strategies of fortification and supplementation in vulnerable groups such as children, pregnant women and the elderly in affluent and developing countries must be based on accurate information concerning the adequacy of different diets and bioavailability with respect to iron. In affluent countries, the trend at present is to consume diets providing low energy with a conservatism in the choice of meals and food components. This trend may create problems in the future.

Zinc

Zinc is probably one of the most important and interesting trace elements related to animal and human health sciences. Just over 150 years ago, the biological significance of zinc was shown by Raulin[23]. In 1905, Mendel and Bradley showed that zinc is a constituent of the respiratory pigment of the snail[24]. A few years later, the work of Birckner indicated a functional role of zinc in higher animals[25,26]. Somner and Lipman in 1926 observed that zinc was essential for plant life[27]. During the early 1930ś, the element was also shown to

be essential for the growth and well-being of rats. An animal disease related to zinc deficiency was described by Tucker and Salmon in 1955[28]. Later, ODell and his co-workers showed the essentiality of the metal in the growth of chicken[29]. The essential role of the metal in human health and disease was described by Prasad and others during the 60's.

The total body content of zinc in an adult human subject is 30-38 mmol (2-2.5 g), which is half the body content of iron and much more than the corresponding figures for any other trace element[5]. The highest concentration of the metal in the body is found in the choroid of the eye and the prostate gland. Human seminal fluid has 100 times the concentration in the blood plasma. Relatively high concentration of zinc is found in the skin of adult humans, and in animals with hair or fur, a considerable amount is found in these tissues. Most of the body zinc in man is found in the bone at a concentration of 3μmol/g (200μg/g), compared with an average of 0.5μmol/g (30μg/g) in fat-free tissues of the rest of the body[5,30].

In blood, zinc is present in erythrocytes, leucocytes and platelets. The concentration of the metal in erythrocytes is estimated to be 0.2-0.25 μmol/ml (10-15μg/ml). Almost 80% of the blood zinc is confined to the erythrocytes. The leucocytes contain 3% of the total zinc in human blood. The concentration of the metal in platelets is estimated to be 10μmol/l (70 μg/l). Human blood plasma /serum contains 12-17 μmol/l (800-1100 μg/l)[5,30]. Most of the plasma zinc is loosely or tightly bound to one of several proteins. The principal zinc-binding protein is alpha2- macroglobulin. Almost 40% of the plasma zinc is bound to this protein, which is not exchangeable. Smaller portions of plasma zinc may bind to proteins such as transferrin[30]. Nearly 60% of the plasma zinc is loosely bound to albumin and as such functions as the main transport protein. Less than 10% of the plasma zinc is bound to amino acids such as histidine and cysteine[30].

As mentioned earlier, zinc is essential to growth, development and normal functions of all living systems. Keilin and Mann demonstrated in 1939 that zinc is an integral part of the enzyme, carbonic anhydrase in red blood cells[5]. Since then, the metal has been found to be an essential component of many enzymes in the liver, kidney, pancreas and many other organs of man and animals. In recent years, it has been found that even the DNA and RNA polymerases are zinc-dependent enzymes[31-32]. During the last few decades, over 200 enzymes dependant on zinc for their activities have been found in various tissues of different animal species[31]. Zinc enzymes participate in a wide variety of metabolic processes, including carbohydrate, lipid, protein and nucleic acid synthesis or degradation[31].

Experimental zinc deficiency in experimental animals' results in a number of abnormalities, including congenital malformation, growth retardation, abnormal bone metabolism, atrophy of the testes, and deformative changes in the skin[5,30,31]. Zinc deficiency hypogonadism, associated with dwarfism, hepatosplenomegaly and geophagia in man is a well-established syndrome today. In patients with leg ulcers, impaired healing is related to zinc deficiency[33,34]. Zinc also plays a key role in the treatment of acrodermatitis enteropathy. Our own findings indicate that zinc may have some protective effects against the toxicity of heavy metals like lead[30]. In vitamin A metabolism, zinc may have a possible role. The metal also has been found to have a role in experimental and human cancers[35]. It has also become evident that zinc is needed for cell-mediated immunity. In experimental human studies, mild deficiency of zinc has shown decreased levels of thymulin, which could be corrected by zinc supplementation[31]. This hormone is involved in the maturation and differentiation of T-cells[31]. Recent data indicates that zinc may directly affect DNA and RNA synthesis[31]. Iwata and his colleagues have shown that one obvious hormonal effect of zinc deficiency results is a reduced number of thymocytes[31]. The gene expression of interleukin-2 and interferon gamma are known to be zinc dependent[31]. Our own studies indicate the involvement of zinc in the pathophysiology of liver disease[36,37]. Recently, zinc has shown to reduce oxidative stress and reduces inflammatory cytokines[31]. Zinc upregulates metallothionein, which is an excellent protein that can effectively scavenge reactive oxygen species. Prasad and his co-workers have shown that zinc supplementation in elderly subjects can reduce oxidative stress and decrease generation of inflammatory cytokines[31].

Like many other trace elements such as iron, copper and selenium, only a small percentage of the dietary zinc is absorbed. The absorption takes place mainly in the duodenum and it is influenced by several factors. Age, individual size, the levels and the chemical form of the dietary zinc, the nutritional status of the individual and the presence of antagonizing substances such as phytates are the major factors affecting the absorption of zinc. Approximately, 20-30% of the ingested dietary zinc is absorbed depending upon its bioavailability[5]. Most of the unabsorbed zinc is excreted in the faeces. The faecal zinc also includes small amounts of endogenous zinc secreted by the pancreas. The urinary excretion of zinc in normal adults is very low when compared with the intake levels. The normal urinary incretion is 1.5-14 μmol (100-900 μg)/ day, but rises markedly in nephrotic syndrome, diabetes, porphyria and alcoholism[5]. Loss of zinc via the skin depends on sweat and is normally

low. Under normal conditions, approximately 5-7 μmol (0.5 mg) is lost via sweat. Under hot climatic conditions, the loss of zinc via sweat can be as high as 50-70 μmol (3-5 mg)/day[5].

Dietary intake of zinc varies considerably in different countries of our globe. Information is also very scant in poor countries in Asia, Africa and South America. The present author and his colleagues have investigated the actual intake of several trace elements employing the double portion technique[35]. The International Atomic Energy Agency in Vienna collaborated with our studies and we have been able to collect information concerned with the actual intake of trace and toxic elements in the diet of average people living in many countries of the world. The data also included the information concerning the intake of trace and toxic metals in the average diets of people living around Chernobyl after the tragic accident. The results of this study were published by IAEA in the early 90ś. Table 2 shows the intake of a few elements in various population groups in Sweden. The study was done in the first place to evaluate the intake and health status of retired people living in their homes in the southern part of Sweden[35].

Our study groups in Sweden included normal healthy adults, retired people, vegetarians, lactovegetarians, pregnant women and teenagers. The intake of most trace elements in vegetarian diets was higher than that found in common diets. The intake of zinc and selenium is equal to or lower than the recommended dietary allowance values.

Until recently, only limited information was available concerning the actual dietary intake of zinc, especially in developing countries in Asia, Africa and Latin America. In 1973, the Food and Agriculture Organization / World Health Organization (FAO/WHO) expert committee provided data concerning provisional requirement of dietary zinc for the first time. This was followed by the recommendations from the National Academy of Sciences in 1974. According to their original recommendations, the daily requirements are 3-5 mg for infants up to the age of 1, 10 mg for children up to 10 years, 15 mg for adolescents and adults and 20-25 mg for women during pregnancy and lactation. These recommended figures, however, have been reduced in recent years as shown in Table 3. Recent studies using isotope studies have indicated a metabolic requirement of 4-6 mg/day[5]. If these figures are accurate, the daily dietary intake in adults ought to be 10-15 mg, considering a 30-40% absorption. Many dietary studies during the last few decades have shown a mean intake of less than 15 mg without any overt sign of zinc deficiency. Most of the reported figures have, however, not considered the important question of bioavailability.

Table 3: Intake of zinc, iron, copper, selenium and lead in Sweden

Element	Intake (mg/μg/day)	RDA* (mg/μg per day)
Iron	12 mg	8 mg
Zinc	8 mg	8 mg
Copper	1-1.5 mg	900 μg
Selenium	30 μg	55 μg
Lead	44 μg	Not available

* Recommended dietary allowances, National Academy of Sciences, Washington DC, 2019

Several studies in affluent countries have indicated that pregnant women are not getting enough zinc through their common diets. A majority of pregnant and lactating women in industrialized countries are receiving much lower than the recommended levels[5]. Low zinc intake together with low plasma levels are associated with complications during pregnancy and at partus[38-40]. Jameson in 1976 reported a few complications in pregnant women with low plasma levels of zinc[39]. When pregnancy is associated with diseases such as diabetes mellitus, the risk for complications is high. It appears that detailed studies of many pregnant women in developing and industrialized countries are necessary for elucidating the effect of zinc during pregnancy and lactation.

Currently, there is no single laboratory test that indicate the body status of zinc. Due to the simplicity and low cost, plasma/serum levels of zinc are traditionally used to assess the body status of the metal. A wide range of factors are known to influence the concentration in plasma/serum levels of the metal and as such are not the best indicator of the total body status. Estimates of zinc in red blood cells, leucocytes and urine can give additional information concerning the body status of zinc. Infections, stress and exercise can influence the plasma/serum zinc[5].

The clinical follow-up of the elderly in Sweden included in our studies showed that the subjects are in good health despite the low zinc intake. Plasma levels were within the normal range. With advancing age, there is usually a reduction in energy metabolism and a deterioration of several physiological functions. Digestive inefficiency is very common in the elderly. Many of them were under treatment with drugs for cardiovascular diseases, respiratory illnesses and diabetes and as such the requirements of zinc may be higher that what is recommended for healthy adults. Summing up from the experience of studies in the elderly, the intake levels of 120 μmol/8 mg/day appears to be adequate. Marginal deficiency, which is hard to detect, may however exist in vulnerable groups such as the elderly and pregnant women.

Copper

Copper is a native element in the earth's crust and thus known to ancient humans. Bronze which is an alloy of copper and tin has been known to humans for at least 5000 years, and the Bronze Age existed until 1000 BCE. There is a wide range of other copper alloys including brass that are in use even at present times[5]. The green colour of the largest copper statue in the world (Statue of Liberty in New York, USA) is due to the oxidation of copper. The main use of copper at present is for electrical wiring, including the windings of electromagnets, transformers and motors.

The presence of copper in biological materials was observed during the early nineteenth century. The element was considered of no importance to biological systems until 1926 when Mc Hargue suggested it's value in the diet of rats[9]. Two years later, Hart *et al* provided the first evidence of the importance of copper in vertebrates[41,42]. They demonstrated that copper in addition to iron was necessary for blood formation in rats. In 1934, Cohen and Elvehjem showed that copper is essential for the elaboration of haem A, a component of cytochrome oxidase[43-45]. During the early thirties, it was observed in several countries that cattle grazing in pastures poor in copper developed anaemia. In other species, osteoporosis or ataxia has been found to be associated with copper deficiency[9]. Copper was found to play a key role in the formation of elastin in animals[45]. Octopuses and many other molluscs use a blue-coloured protein called hemocyanin for the transport of oxygen. These organisms have blue blood instead of the red found in other organisms. Many pathogenic bacteria, viruses and fungi can survive for long intervals on all surfaces, but when coated with copper, they are eliminated very fast.

The average human adult body contains 1.3-1.9 μmol (80-120 mg) of copper[5,9]. In comparison with the amounts of iron and zinc, the copper contents in the adult body are 20-50 times lower. About a third of the body's copper is found in the liver and brain. In new-born infants, hepatic copper is several times higher than in adults[46]. Redistribution of the hepatic copper takes place during the first four years of life[47]. Exceptionally high concentration of copper is found in the pigmented parts of the eye[9]. Skeletal muscle due to its high mass contains about 1/3 of the total body copper[47].

Copper in blood is found mainly in erythrocytes and partly in plasma. In erythrocytes, the metal is bound to erythrocuprein (super oxide dismutase) at a concentration of 54 nmol (3.4 μg/mg) of the protein. This protein found in all cells of the body eliminates the superoxide radical. The rest of the erythrocyte copper is loosely bound to non-specific proteins. In the plasma, nearly 90-95% of the metal is strongly bound to ceruloplasmin and thus, it is very stable[5,9]. The rest is loosely bound to albumin. The equilibrium of copper in the intra and extracellular fluids is brought about by the albumin-bound copper. Ceruloplasmin with a molecular weight of 130,000 Daltons has a very intense blue colour and each molecule contains 6 copper atoms[48]. Plasma copper levels are slightly higher in females than in males. Normal values are around 16μmol/l (1mg/l), which is almost the same as that of iron and zinc[5,9].

As mentioned above, copper is a constituent of many vital enzymes, including cytochrome oxidase, dopamine beta hydroxylase, urate oxidase, tyrosinase, lysyl oxidase and superoxide dismutase[5,49]. In several animal species, copper is found to be essential in such diverse activities as heme synthesis, connective tissue metabolism, bone development and nerve function. Copper deficiency in experimental animals results in anaemia, abnormalities of hair and skin pigmentation and impaired immune functions[5,9]. Many reactions of copper in animal and human metabolism take advantage of its redox potential. This is the ability to cycle back and forth between the oxidised states, divalent to monovalent copper. From a nutritional point of view, copper metabolism is not affected by the presence of other micronutrients except zinc. From a pharmacological point of view, high zinc is known to block the absorption of copper[5,9].

Two types of inherited copper accumulation diseases are well documented. They are Wilson's (WD) and Menkes diseases. Wilson's disease is an inherited, autosomal recessive disease of copper accumulation and toxicity[50]. The normal biliary excretion pathway of copper is failed in this disease through the mutation of the ATPase enzyme (ATP7B). The copper absorbed is accumulated in the liver and patients with WD end up with liver disease. They often have hepatitis and jaundice. About 50% of patients with WD develop brain disease with neurological movement disorder. WD is rare and currently, there are 10,000 patients in the US suffering from it. Treatment with penicillamine and Trientine which are metal chelates enhance the excretion of copper in urine. Thiomolybdate are also used in the treatment of WD. In recent decades, Brewer and his colleagues have treated WD patients with zinc and results are very good[51]. Menkes disease in 1962 described a sex-linked disorder with kinky hair-restorer growth and brain damage related to a defect in copper absorption[51]. Vulpe *et al* in 1993 showed that the genetic cause was in the gene called ATP7A[52]. This gene is on the X-chromosome and defects in it produces sex-linked disorders[50,52]. One key role of this protein is in the intestinal cell involving the transport of copper from the cell to blood. It is also involved in the transport of copper from blood to cerebrospinal

fluid. Copper levels are low in blood and the diagnosis is difficult. Treatment is often with salts of copper given early after birth, once the diagnosis has been made. Another ATP-7A disease like Charcot-Marie-Tooth disease which causes motor neuropathy is described by Kennerson *et al*[53]. This results in progressive distal motor neuropathy without prominent sensory loss. There is no treatment for this disease at present and copper therapy is not recommended. In recent years, the prevalence of Alzheimer disease in developing countries has been found to correlate to high copper intakes[50] through drinking water and oral supplementation. Increased meat eating also has been shown to correlate with high copper intakes. In Indian childhood cirrhosis, excessive dietary copper has been postulated to have an etiological role[54]. Increased copper accumulation is also found in primary biliary cirrhosis and prolonged extrahepatic biliary tract obstruction[5].

The ingested copper is mainly absorbed from the duodenum in man. Various estimates indicate that about 30% of the dietary copper is absorbed[5,49]. The absorption of the metal may proceed through an active transport or through a carrier-mediated mechanism[9,55]. Metallothionein is thought to be involved in the absorption of copper[56]. The absorption of copper is antagonized by several dietary components including ascorbic acid, divalent cations such as zinc and cadmium and phytate[5,9]. The major portion of the unabsorbed copper is excreted in the faeces. The normal excretory pathway is via the bile. Only small amounts are lost in urine, skin and hair. Our studies, as well as the studies of others, indicate an average daily intake of about 2 mg copper, which is close to the current recommended levels[5]. Vegetarian diets provide almost double the amount of copper compared to the common diets[5]. A pure nutritional deficiency of copper is rare in human adults. A few cases of anaemia in malnourished children are attributed to low levels of copper and ceruloplasmin in blood. Copper deficiency may also occur in patients receiving long-term parenteral nutrition. In such patients, anaemia and leukopenia are observed, which are reversed by copper therapy. As mentioned earlier, consumption of high quantities of zinc for prolonged periods can result in secondary copper deficiency[5,49]. The relatively high intake of calcium found in the common diets of adults in affluent countries may aggravate the copper homeostasis by inhibiting its absorption.

Selenium

Selenium was discovered by the Swedish scientist Berzelius in 1817 during the oxidation of sulphur dioxide from copper pyrites in the production of sulphuric acid[5]. It has both metallic and non-metallic properties. This element was initially considered important only based on its toxicity. Already in 1842, Japhs described the toxicity of selenium in animals[9]. Almost a century later, selenium toxicity was found to cause specific diseases in livestock[5,9]. Plant-induced neuropathy in grazing horses and cattle in the US during the 1930's was associated with selenium toxicity[9]. In 1957, Schwarz and Foltz could show that liver necrosis in vitamin E deficient rats responded positively to treatment with traces of selenium in the diet[57]. After this important discovery, considerable attention was focused upon the physiological role of selenium. During the late 1950's, it was also observed that several diseases in animals with vitamin E deficiency such as white muscle disease, heptoses, alopecia and infertility responded positively to vitamin E/selenium therapy. Towards the latter part of 1960's, it was equivocally established that selenium is an essential micronutrient in animals[5,9]. In the meantime, studies were in progress with regards to the essentiality of the element in man. During the 1970's, several researchers have shown that the growth of human fibroblasts was influenced by selenium[5,9]. Awasti *et al* in 1975 purified glutathione peroxidase from human erythrocytes and found that selenium was an active component of the enzyme[58]. In 1979, Van Rij *et al* reported positive effects of selenium supplementation in a patient with muscular discomfort on long-term parenteral nutrition[59]. Finally, the importance of selenium in human nutrition was shown in studies of children with cardiomyopathy in China[5,60].

Total body contents of selenium in a healthy adult is estimated to be 60-90 μmol (5-7 mg). The kidney cortex contains the highest concentration of the element followed by the liver and thyroid tissues[5,9]. The lowest concentration of the element is found in the fat tissue. Selenium in blood is distributed partly in erythrocytes and partly in plasma. Oh *et al* in 1974 showed that 75% of the total ovine red cell selenium is found in the enzyme, glutathione peroxidase[61]. Plasma selenium is bound mostly to alpha and beta globulins non-specifically, although some of it is also bound to glutathione peroxidase[5,9]. Analysis of selenium in the blood of Canadians showed that 2.3 μmol (3 μmol (236μg)) is in whole blood, and 1.8 μmol (144 μg) in plasma[5]. Allaway *et al* in 1968 showed a mean value of 2.6 μmol (286μg) in the whole blood of subjects living in seleniferous areas[62]. Kasperek *et al* found a mean value of 1.2 μmol (98 μg)/l. In general, the concentration of the element in whole blood and plasma varies greatly in different parts of the world, from below 0.25 μmol (20 μg)/l in China where Keshan disease is prevalent to over 3.8 μg (300 μg)/l in subjects living in parts of Venezuela where the soil is rich in selenium. In New Zealand, Sweden and Finland where

the soil is poor in selenium, the blood levels in general population are around 0.6 - 1.2 μmol (50 - 100μg)/l[5,9,63].

The dietary selenium is rapidly and efficiently absorbed from the gastrointestinal tract depending upon the amount and chemical form of the element[5,9,63]. Studies employing radioisotopes indicate that the duodenum is the main site of absorption in animals. Studies in New Zealand indicate that while selenium in the form of Selenomethionine is absorbed almost completely, only 60% of the ingested element is absorbed when it is in the form of selenite. Christensen *et al* in 1983 showed that selenium in poultry meat is better absorbed than selenite[5]. The absorbed selenium is usually converted to selenide and incorporated in proteins as selenocysteine and selenomethionine. Selenide also can be converted to dimethyl selenide, which has a garlic-like smell. When the intake is high, the dimethyl selenide formed can be lost through exhalation and the garlic-like smell can be easily detected. The excretory pathway of the absorbed element is via urine as trimethyl selenium. Smaller amounts of the absorbed element is lost in sweat[5,9,63]. The unabsorbed selenium is excreted in the faeces. The concentration of selenium in hair and toenails has been used in epidemiological studies to assess the selenium status due to simplicity and low cost for storage[5].

Despite its toxicity, selenium is an essential element for plants, animals and humans. Several studies have reported that high selenium status is associated with low overall mortality[5,9,64]. The nutritional role of selenium is related to a group of melanoproteins with redox activities. One of the known functions of selenium is its role in the enzyme, glutathione peroxidase. This enzyme mediates as an antioxidant and thereby protects cell membranes. Several studies in experimental animals have shown that selenium interacts with vitamin E[5,9]. It may cause several diseases in animals including liver necrosis. Striking pallor and the degeneration of skeletal muscles resemble manifestations of vitamin E deficiency, and these abnormalities can be ameliorated by the dietary supplementation of sulphur-containing amino acids. The fact that selenium is an integral part of glutathione peroxidase in erythrocytes and other tissues partially explains the interrelationship between the element and vitamin E. Moreover, selenium resembles sulphur in many aspects, although it is not clear at present whether selenium can replace sulphur in important metabolic reactions. Selenium may also take part in other activities such as the maintenance of sperm vigour and motility, muscle integrity, involvement in nucleic acid metabolism and participation in pancreatic functions[65-79]. In heavy metal poisoning, selenium has been found to reduce the toxicity considerably[5,9,64]. Recent epidemiological studies indicate that the deficiency of the element is associated with several diseases including cardiovascular diseases, cancer, rheumatism and multiple sclerosis[65-79].

From geochemical and toxicological points of view of the known essential trace elements, selenium is the least abundant in nature and it is irregularly distributed in the soil of our planet. Because of this, selenium contents in food varies significantly in different geographic areas. Australia, New Zealand, certain parts of North America and Scandinavian countries are known to have considerably low contents of selenium in the soil. On the other hand, some countries in South America, especially Venezuela, is rich in selenium in the soil. In countries with low selenium in the soil, a minimum supplementary intake of the element is recommended for domestic animals[5,9,63]. A working group within the Scandinavian Agricultural Research Association has recommended a minimum intake of 1.3 μmol (0.1 μg) selenium per kilogram fodder in common domestic animals[5]. Selenium appears to have no biological function in plants and any selenium found in plants reflects the concentration of selenium in the soil. The capacity of plants to accumulate selenium depends on the pH of the soil and the presence of several other elements. Selenium contents of the cereals may vary 1000-fold depending upon the location of the grain grown. On the other hand, selenium is known to be essential for birds and domestic animals and hence the meat for human consumption always has some selenium. Selenium contents in eggs, milk and meat usually reflect the concentration of the element in plants and grain eaten by the animals and birds, which is the source of these food items. Supplementation of the soil and animal fodder is expected to increase the concentration of selenium in the meat of domestic animals. The supplementation of animal fodder with selenium in Sweden, however, has not resulted in any significant increase in the levels of the element in the liver and meat of pigs[5].

Studies in Sweden by Abdulla and others showed an average intake of 40 μmol (30 μg)/day[5]. The vegan diets had the lowest concentration of around 13 μmol (10 μg)/day. The vegan diets consisted mainly of green vegetables grown locally. As mentioned earlier, selenium is not essential for the growth of plants, the concentration of the element in daily diets of selenium reflects the amount of selenium in the soil where the vegetables are grown. Like the soil in Australia and Finland, the soil is poor in selenium. Some vegans consumed nuts imported from other countries and they had a higher intake of selenium than those who consumed lesser amounts of the element[5,80]. The lacto-vegetarian diets on the other hand had higher amounts of the element compared with the common and vegan diets. The main reason for this increase was

due to high contents of imported food items as well as the high consumption of dairy products[81]. The diet of teenagers contained almost the same amount of selenium as found in the common diets[5].

Selenium status is usually assessed by the concentration of the element in blood and the activity of the enzyme, glutathione peroxidase in the erythrocytes. The concentration of the element in the blood normally reflects the dietary intake[5]. The body status of the element is also estimated from its concentration in erythrocytes, plasma, hair and nails. The selenium levels in plasma indicate only a short-term body store[5,74]. Analysis of selenium in the hair is a good alternative when bold samples are difficult to obtain, especially in children. There appears to be a good correlation between the blood levels and hair contents[5,9,74]. Although the activity of glutathione peroxidase in erythrocytes has been used in the past as a measure of biological activity of selenium, there is a growing awareness concerning the presence of other glutathione peroxidase which are not selenium dependent. Glutathione peroxidase activity in platelets may be a better indicator of selenium status than that is found in erythrocytes.

The blood levels consuming common diets in Sweden showed values ranging 38-96 μmol (30-76 μg). Similar values are found in the blood of healthy Finnish people[5,63]. The population consuming a pure vegan diet has somewhat lower levels in the blood[80]. They did not, however, manifest an overt sign of selenium deficiency. Clinical follow-up of the elderly in Sweden also did not show any signs of selenium deficiency. It appears that the populations in countries with low selenium levels in the soil have adapted to the low selenium levels in the diet. As in the case of other trace elements like zinc and copper, subclinical deficiency which is difficult to detect at an early stage may occur in vulnerable groups, especially in developing countries. Only time can predict whether the general population living in countries with low selenium levels in the environment have an adequate selenium status or not. Studies are in progress in China and elsewhere.

Lead

Lead has been used by mankind in a variety of ways throughout historical times and it is one of the seven metals of antiquity (gold, mercury, copper, iron, tin and silver are the others). The ancient Greeks, Romans and Alchemists thought the metal was associated with the planet Saturn[5]. The ancient Egyptians smelted lead and used it in pigments, cosmetics and medicine. Lead compounds are still used in eye-makeup in several countries in Asia and Africa. The ancient Romans also made use of lead in the preparation of medicines, even though they knew about the toxicity of the metal. Lead played a crucial role in the invention of printing press during the fifteenth century. Many ancient uses of the metal in pottery, paints, glazes and enamels and medicines have been declining steadily over the last few decades due to their discharge in the environment and toxicity. Lead is also used at present as shielding in X-ray machines. During the last few decades of the 20th century, 5-10% of the total lead produced in the world was used in gasoline, a practice which is diminishing at present. The lead present in gasoline is eventually discharged into the human environment. It may be inhaled or ingested through various foodstuffs, especially the green vegetables. In the US, the use of anti-knocking agent (tetra-ethyl lead) is prohibited since 1986. Lead compounds are also extensively used in the production of storage batteries and as stabilizers and pigments in plastics. The metal is also used in certain alloys and in the manufacture of crystal glass. Ship and car destruction plants represent another source of lead exposure. At high temperatures as observed during welding and cutting operations, lead is emitted from materials coated with lead-containing paints. Lead salts are also used frequently in pottery industry during the last few centuries. Food and beverages occasionally become contaminated by lead from glazes of earthenware used in the household. Food materials kept in soldered cans for future consumption is another source of lead exposure, especially if the material stored is acidic. In 2014, the annual production of lead was over 10 million tonnes.

An adult human body contains 0.4-2.0 mmol (90-400 mg) of lead, of which 90% is in the skeleton. The levels of the metal in tissues rises when the intake is high, especially in bone, liver and hair. The concentration of lead in blood varies from country to country and the average values are estimated to be around 80 μmol (165 μg)/l[5,9]. The blood contents in adults living in the southern part of Sweden has been found to be 48 μmol (100 μg)/l, which is somewhat lower than that found in the blood of adults living in other parts of Europe and the United States. The ingested lead is poorly absorbed, and the major route of excretion is via faeces. The normal absorption in most healthy subjects has been found to be 5-10% of the ingested levels. A small amount of the ingested lead is lost in sweat, urine and nails. A small amount of lead is found in the milk of lactating women. Absorption of lead in children is higher than that observed in adults. Certain nutrients such as calcium, zinc, phosphorus and vitamin-D are known to influence the absorption of lead[82-84].

The major pathway through which lead enters the human body is via food and drinks. Cigarette smoking may also contribute a significant amount of the

metal to the total human body burden. Most dietary components normally contain only traces of lead, except where the soil is contaminated with lead and food items are cultivated in such areas. Only limited data is available at present regarding the contents of the metal in prepared meals ready for consumption. Intake levels based on the expected levels of lead in food, air, water and from smoking in USA and Europe during the mid-1960's indicate approximately 1-2 μmol (400-200 μg)/day[9]. Studies in Sweden indicate a much lower intake than that found in other European countries. Somewhat higher levels are found in the diet of Finnish population[5]. The low dietary intake of lead in the general population of Sweden reflects the low blood levels found, compared to the reported values in Europe and USA. The dietary intake can also be extrapolated from the concentration found in the faecal excretion and such results are also in agreement with the lower intake of the metal in Sweden. The provisional standards set by the FAO/WHO for tolerable intake of lead per week is 0.24 μmol (50 μg)/kg body weight. Consumption of illicit liquor and wine may contribute considerably to the body burden of lead. Many of the common wines sold by the liquor shops in Sweden and Europe may contain as much as 6-5 μmol (1.2-1.1 μg) lead/l. Thus, consumption of a single glass of wine may provide the same amount of lead as found in the rest of the diet[5].

Biological effects

Lead is a toxic metal that affects every biological system in the human body. The metal is a cumulative toxic substance. Children are more vulnerable than adults. The metal affects most organs of the human body and manifest a variety of biochemical defects. The central nervous system of young children is very sensitive to the toxicity of lead. The other systems of the body that are affected by lead toxicity are the haematopoietic, cardiovascular, renal and gastrointestinal systems. A short summary of these disorders will be provided in the following paragraphs. In addition to the human data available at present, we have the results of many animal studies that demonstrate the toxic effects of the metal. Like many other toxic metals, lead inhibits the activity of several important enzymes, especially those with sulfhydryl groups. Mitochondrial functions are known to be affected by lead. Occupational exposure to high levels of lead induces neuropathy and nephropathy. High chronic exposure to lead may also result in the development of hypertension and other cardiac complications[5,9]. Lead exists in three stable isotopes. The most common isotope is lead-208 which happens to be heaviest stable nucleus of any element. The only lead isotope that has been on earth since the planet formed is lead- 204 which is an unstable isotope. The most important health effects of lead are given below.

Hematopoietic effects

Chronic lead exposure often results in mild anaemia with shortened lifespan of red cells. It is also associated with reduction in reticulocytes and the presence of basophilic cells in the peripheral blood. Heme synthesis in man and animals require several enzymes and three of the seven enzymes required for heme synthesis are downregulated by lead[5,9]. Delta aminolaevulinic acid dehydratase (ALAD) is the second enzyme that regulates the synthesis of haemoglobin in humans. This enzyme catalyses the condensation of two molecules of ALAD to one molecule of porphobilinogen. In aerobic cells, porphobilinogen is a specific precursor of porphyrins. ALAD is thus a very important metabolic control point in heme synthesis. The rate limiting enzyme in heme synthesis is ALA-synthetase present in the mitochondria. The toxic effect of lead in heme synthesis starts at very low concentrations. Depressed haem synthesis usually stimulates ALA-synthetase, which increases the levels of delta aminolaevulinic acid in blood and urine. Anaemia in lead-exposed populations is observed only when the lead levels are very high[83-92]. Basophilic stippling in erythrocytes is often observed in the early phases of lead poisoning.

Effect on the cardiovascular system

During the last few decades, several studies conducted in various parts of the world have indicated a small increase in blood pressure in populations with increased exposure to lead[93-95]. Since most of the epidemiological studies were cross-sectional, it is difficult to conclude the casualty of blood pressure to lead exposure alone. At the same time, even a weak association with an increase in blood pressure due to lead toxicity is a matter of very important public health concern. In several human and animal studies, lead toxicity has been found to be associated with several morphological and biochemical changes leading to diseases in the cardiovascular system. These changes are often age and sex related. The exact mechanisms by which lead influences the cardiovascular system, however, are not very clear now. Some studies indicate that the inhibition of cytochrome P450 and superoxide dismutase by lead may result in the alteration of lipid metabolism. These changes are known to be associated with the risk of developing cardiovascular diseases[5,9,95-99].

Effect on the neurological system

The central nervous system, especially in infants and young children, is one of the most vulnerable targets for lead toxicity. Many of the affected children may suffer

from permanent neurological damage. One of the serious effects of lead toxicity is acute encephalopathy with serious neurological complications. This happens when the exposure levels are very high. In children dying from acute encephalitis, the major changes are found in cerebellum and in capillary endothelial cells[100-109]. Peripheral neuropathy is another health effect seen in chronically lead exposed individuals. Studies in the United States a few decades ago indicate that more than half a million children are neurologically affected by lead poisoning. Many of these children may suffer from permanent damage to the nervous system. Infants and children who recover from encephalopathy due to lead poisoning are prone to mental retardation, epilepsy and optical neuropathy. The manifestation of lead toxicity on the peripheral nervous system includes reduced motor activity and co-ordination[95,104]. Among the most important ways that the metal affects the nervous system are those involving the interferences with calcium- dependent reactions and/or disruptions of calcium homeostasis[95-104]. Lead may also inhibit neurotransmission. The vulnerability of fetuses and infants due to lead toxicity may be due to the immaturity of the blood-brain barrier and the lack of high-affinity lead binding proteins in the astroglia[95].

Effect on the renal system

Tubular dysfunction is one of the early manifestations of lead toxicity in kidneys. In children with acute lead poisoning, the tubular dysfunction is reversible. In chronic exposure, renal tubular functions are irreversible and results in vascular sclerosis, tubular cell atrophy, interstitial fibrosis and glomerular sclerosis[5,9,95]. Long-term exposure to lead results in chronic nephropathy. During the early phase of chronic exposure to lead, the major effect is on renal tubules. It is pronounced in proximal tubular cells. This in turn results in aminoaciduria and glycosuria. The development of hypertension in lead-exposed individuals mentioned earlier is probably through the damage on tubular cells. Since lead reduces the excretion of uric acid, there seems to be some evidence for the development of gout in lead-exposed individuals[5,9,95,100,110]. The symptoms from the kidneys after exposure to lead is often subtle. Symptoms of lead poisoning in the kidneys often appears when significant reduction in renal functions have occurred.

Effect on other organ systems

In addition to the various organ systems mentioned above, lead may also have effects on other organ systems including the immune system, bone cell function and reproductive system. Both humoral and innate immunity is impaired in experimental studies. There is, however, no change in the levels of immunoglobulins after lead exposure. Little is known about the effect of lead on reproductive and endocrine systems. Like other heavy metals, lead influences the uptake of iodine. Experimental studies indicate that lead may injure the primary thyroid axis. The function of pituitary-adrenal axis is impaired in patients intoxicated with illicit liquor. Several recent studies indicate no effect on sterility, pregnancy and abortion in women exposed to lead. Bone is the largest reservoir of body lead. The exchangeable skeletal lead pool is very small. Age, endocrine status, osteoporosis and renal disease are some of the factors affecting the mobility of the metal from bone. The extent of lead exposure in the general population is estimated by measuring the contents in teeth and fingers. Lead is categorized as a category 2B carcinogen[110-113]. A few experimental studies indicate the development of renal adenocarcinoma after exposure to lead for long intervals. No epidemiological studies are reported indicating the incidence of cancer and lead exposure[114].

In short, the health effects of lead have been described. Control of the environmental exposure is absolutely the most important method of prevention. Chelation therapy is another method for preventing lead toxicity, especially in children[115,116].

CONCLUSION

In this review, I have covered the health effects of a few selected trace elements such as iron, zinc, copper, selenium and the toxic metal lead. The other elements which are of clinical and public health interest are arsenic, cadmium, chromium, cobalt, iodine, manganese, mercury, molybdenum, nickel, silicon, tin, vanadium and probably others. For additional information regarding these elements, the reader is directed to standard textbooks on trace metals.

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Original Article

Can fracture location in relation to the olecranon fossa predict postoperative deformity in displaced pediatric supracondylar humerus fractures?

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ABSTRACT

Objective: We aimed to examine the location of the fracture line according to olecranon fossa in displaced pediatric supracondylar humerus fractures. We wanted to know if there is a relation between necessity of open surgery and postoperative coronal and sagittal plane deformity rates or not.
Design: Retrospective study
Setting: Department of Orthopedic and Traumatology, Prof. Dr. Cemil Taşçıoğlu City Hospital, Turkey, between 2010 and 2020
Subjects: One hundred and twenty-two patients with Gartland type 3 supracondylar humerus fracture
Intervention: One hundred and twenty-two pediatric patients who underwent surgery with Gartland type 3 supracondylar humerus fracture with extension deformity were examined retrospectively.
Main outcome measures: Surgery type, localization of fracture line according to olecranon fossa, postoperative varus-valgus deformity, and postoperative flexion-extension deformities were noted.
Results: Fracture line according to olecranon fossa level passed through the lower 1/3 in 12 cases, through the middle 1/3 in 25 cases and through the upper 1/3 in 85 cases. There was no statistical significance between localization of fracture line according to olecranon fossa and open reduction rates (P=0.56). Varus rate was higher in patients with lower localization of fracture line according to olecranon fossa (41.7%) compared to patients with middle (12%) and upper (2.4%) level (P<0.001). Extension deformity rate was higher in patients with lower localization of fracture line according to olecranon fossa (33.3%), and flexion deformity rate was higher in patients with middle localization (8%) (P=0.001).
Conclusion: Evaluation of fracture line level according to olecranon fossa may provide the surgeon estimating the possibility of postoperative coronal and sagittal plan deformity.

KEY WORDS: fracture line, humerus, olecranon fossa, pediatric, supracondylar

INTRODUCTION

Pediatric supracondylar humerus fractures represent 60% of all elbow fractures and 3% of all childhood fractures[1]. These factures are pediatric elbow fractures and they can be difficult to treat[2].

Closed reduction and pin fixation are the treatment methods preferred in displaced pediatric supracondylar humerus fractures. However, the number of open surgeries after insufficient closed reduction reaches up to 70%[3]. In these fractures, ensuring anatomic fracture restoration and percutaneous pinning result in full range of motion of the joint and low complication rate[4].

Supracondylar fractures are generally seen in coronoid and olecranon fossa level, just above the fossa or in the distal metaphysis of humerus including the thin section of the humerus[1]. Coronoid fossa is located anterior, and olecranon fossa is located posterior between the lateral and medial edges of distal humerus[5]. When the anatomy of the elbow is examined, it could be seen that lateral and medial columns of the humerus have a narrow surface area in the sagittal plane at the level of both fossae[6].

Our hypothesis is that this anatomical narrowness in the sagittal plane can cause difficulties in closed reduction and/or anatomical reduction in fractures

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seen in this area. This could result in more coronal/sagittal plane deformities and/or higher open reduction for failed closed reduction in the postoperative period. The aim of the study is to examine the location of the fracture line according to olecranon fossa where the humerus narrows down in the sagittal plane and to address whether there is a relationship between the requirement of open surgery and postoperative coronal and sagittal plane deformity rates.

SUBJECTS AND METHODS

Files of 243 patients operated due to pediatric distal humerus fracture at orthopedics and traumatology clinic of our hospital between January 2011 and December 2020 were examined retrospectively. Of these patients, 122 of them were pediatric cases who underwent surgery with Gartland type 3 supracondylar humerus fracture with extension deformity. Patients with surgical intervention time exceeding 24 hours, open fractures, flexion type fractures, Gartland type 1 and type 2 fractures, type T fractures, medial and lateral epicondyle fractures, fractures with neurovascular deficit, multiple part fractures, pathological fractures and patients with additional injuries and patients under the age of three were excluded from the study because they would affect radiographic assessments.

Surgical decisions for the patients were taken by the senior specialist who was responsible for the emergency cases of that day. Moreover, these cases were operated by the same surgeon. All of the cases were operated under general anesthesia and in supine position. In cases with closed reduction, reduction was obtained under fluoroscopy. Then, percutaneous fixation was achieved with Kircshner wires (K wires) according to the surgeon's preference. While a person ensured the continuity of the reduction, the pin was applied from the medial and/or lateral condylar sides by the surgeon. When the medial pin was applied, mini open surgery was preferred. Then, fixation was ensured by K wires upon the preference of the surgeon. In all cases, the distal part of the wires was left out of the skin in order to avoid a second anesthesia application.

Unless the desired reduction could not be achieved after 3 to 5 closed attempts, open reduction was applied. In cases where open reduction was applied, one of the incision methods including single lateral, single medial, lateral + medial double incision or posterior incision was used according to the surgeon's preference.

After surgery, a long arm splint cast was applied to each patient to release the metacarpophalangeal joints and the forearm brought in a neutral position (elbow in flexion with 30-60 degrees). If postoperative roentgenograms were normal, finger exercises were instructed to the patients and their discharge was planned after 24 hours if there was no swelling. After three weeks, they were called to the first follow-up. Direct radiographies were scanned, the splints were removed, and passive range of motion (ROM) exercises were allowed. Ten days of follow-up was ensured with outpatient clinic controls, and K wires of cases upon radiological and physical examination were removed under outpatient clinic conditions (during postoperative 4-6 weeks). Then, active ROM exercises were initiated. Deformity measurements were made on roentgenograms taken one month after the removal of K wires.

The angle between lateral condylar physis and humerus shaft was measured for Baumann angle. Values between 64° and 81° were accepted as normal[7]. A range between 45° and 57° was accepted as normal for lateral Capito-humeral angle[8]. Values out of these ranges were assessed as deformities.

Measurements of fracture line according to olecranon fossa were made from postoperative control roentgenograms taken when the patient was taken out of the surgery room. Radiographic measurements were taken by imaging software used in our hospital named INFINITT PACS (Picture Archiving and Communication Systems) version 3.0.11.4 (BN13). Required classifications were made by enlarging distal humerus 10x by means of this software since it was hard to divide olecranon fossa to three parts in its normal image magnification. Averages of measurements were taken by two different surgeons who did not perform the surgeries. Numerical values identified based on these measurements were used in statistical calculations as data[9]. Locations of fracture line according to olecranon fossa was performed twice by these surgeons at different times. In cases where there was a disagreement between the surgeons, a mutual decision was taken upon the evaluation performed by them. At the same time, intra-observer and inter-observer reliabilities of fracture level according to olecranon fossa was evaluated by the two surgeons.

When the fracture line was determined according to olecranon fossa, two lines were drawn perpendicularly to the humerus shaft connecting outer cortexes of humerus (lines 1 and 2). Then, line 3 was drawn to perpendicularly connect middle points of these two lines (the line representing anatomical axis of humerus shaft). Upper and lower points of olecranon fossa were determined on this line. A circle representing the olecranon fossa formed by upper and lower points was drawn since olecranon fossa was not a full circle. Then, diameter was measured and divided into 3 equal parts. Two lines were drawn perpendicularly to the

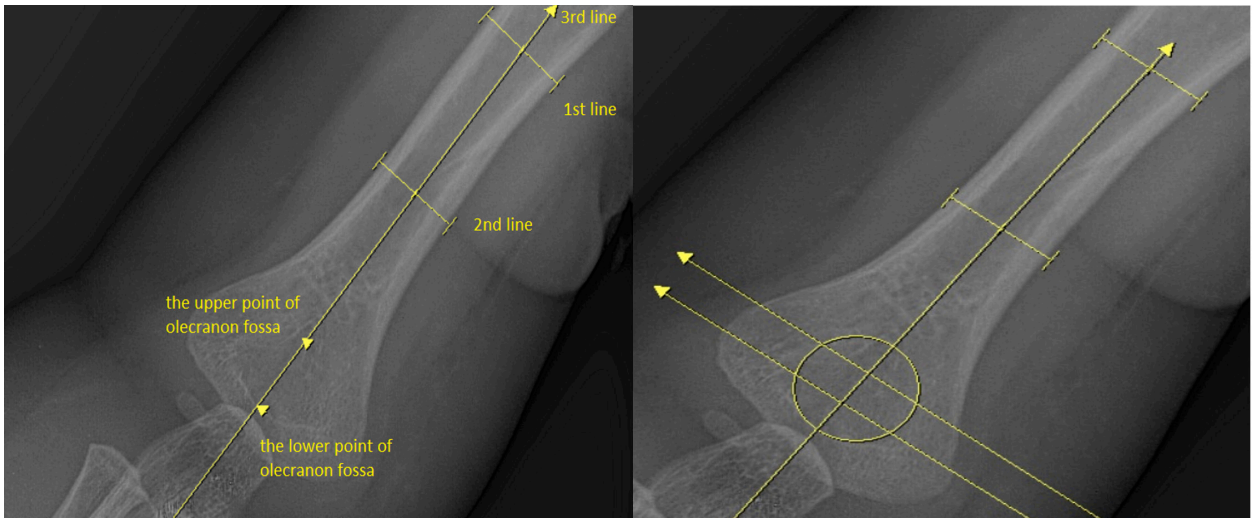

Figure 1: Lines 1 and 2 were drawn perpendicularly to the humerus shaft connecting outer cortexes of humerus. Line 3 was drawn to connect middle points of lines 1 and 2 perpendicularly. Upper and lower points of olecranon fossa were determined on the line (left). The diameter of representative olecranon fossa formed by upper and lower points was drawn. Representative olecranon fossa was divided into 3 equal parts with lines drawn perpendicularly to line 3 (right).

line representing the anatomical axis of the humerus passing from the points dividing these parts (line 3), and representative olecranon fossa was divided into 3 equal parts (Figure 1).

If fracture line goes through upper 1/3 or above the olecranon fossa, it is defined as upper; if it goes through middle 1/3, it is defined as middle; and if it goes through lower 1/3, then it is defined as lower (Figure 2). In oblique fractures, the level where more than 50% of fracture line was seen was used to categorize the fracture level.

Factors such as presence of medial spike at distal fragment, the surgeon performing the surgery and multidirectional instability in surgery of pediatric supracondylar fractures to be effective on reduction type; surgeon and obesity to be effective on postoperative deformities were included in the study[9-13].

Cases with body mass index (BMI) ≥ 25 were classified as obese[9]. Cases were classified as posterior, posteromedial and posterolateral based on displacement direction of distal fragment[10]. During

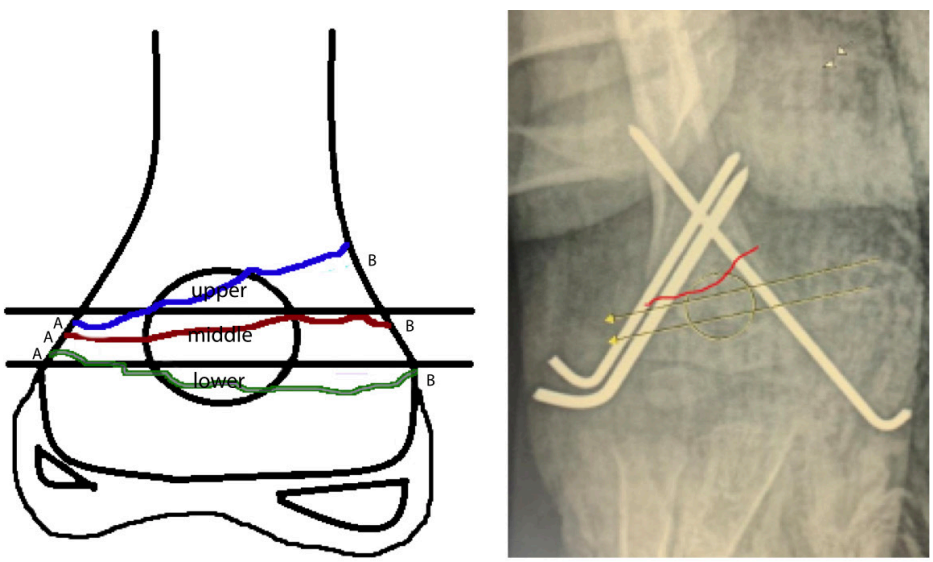

Figure 2: Olecranon fossa was divided into 3 equal parts in AP radiography. Fracture line was categorized as upper, middle, or lower based on the part in which it was located when passing through fossa (left). In the X-ray, it has been observed that the fracture line of the patient passed through upper level of olecranon (red line: fracture line) (right).

closed reduction, unstable fractures changing location both in flexion and extension under intraoperative fluoroscopy were recorded as multidirectional instability[11]. Surgeries were performed by 10 different senior surgeons. All of the surgeons had over 5 years of experience in trauma surgery field.

Age, sex, surgery type (open-closed), Baumann angle, lateral capito-humeral angle, location of fracture line according to olecranon fossa, surgery duration, postoperative varus-valgus deformity presence, postoperative flexion-extension deformity presence, BMI, surgeon performing the surgery, medial spike presence, direction of distal fragment and malreduction rates multidirectional instability presence were noted, and the data were evaluated statistically.

Statistical analyses were performed with SPSS version 22.0 software. Conformity of variables to normal distribution was examined with histogram graphs and Kolmogorov-Smirnov test. When descriptive analyses were performed, average, standard deviation, median and minimum-maximum values were used. 2x2 matrix was compared with Pearson Chi Square and Fisher's Exact Tests. Mann-Whitney U Test was used for the assessment of nonparametric variables not showing normal distribution between groups of two, while Kruskal Wallis test was used for the assessment between more than two groups. K-statistics were used in order to create a relative level of agreement between observers for two readings and between separate readings of the same observer. Data were interpreted according to Landis and Koch. An agreement was scored as mild (kappa = 0-0.2), fair (kappa = 0.21-0.40), moderate (kappa = 0.41-0.60), significant (kappa = 0.61-0.80) and almost excellent (kappa = 0.81-1). Cases where *P*-value was under 0.05 were assessed as statistically significant.

Ethical approval

The study was approved by Ethical Review Committee of University of Health Sciences Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey.

RESULTS

Totally, 75 boys (61.5%) and 47 female (38.5%) cases were included in the study. Average age was 6.38±2.78 years and average surgery duration was 54.77±24.16 minutes. Open reduction was applied to 38 patients (31.1%). Average surgery duration of open surgeries (78.47±25.93 min) was longer than closed surgery (44.05±13.34 min; *P*<0.001). Average Baumann angle and lateral capito-humeral angle were 70.61±8.16 degrees and 55.21±12.64 degrees, respectively. Postoperatively, ten patients had varus (8.2%) and 16 patients had valgus (13.1%) deformity. Furthermore, five patients had postoperative flexion deformity (4.1%) while nine patients had postoperative extension deformity (7.4%).

Upon evaluation of the localization of the fracture line according to olecranon fossa as performed by observers on the same radiography images with 2 weeks in between and independent from each other, the inter-observation coherence was good for both observers (observer 1: κ 0.721, observer 2: κ 0.647). There was a moderate level of coherence between the measurements between observer 1 and 2 (κ 0.530).

Fracture line according to olecranon fossa level passed through the lower 1/3 in 12 cases, through the middle 1/3 in 25 cases and through the upper 1/3 in 85 cases. There was no statistical significance between localization of fracture line according to olecranon fossa and open reduction rates (*P*=0.56). Varus rate was higher in patients with lower localization of fracture line according to olecranon fossa (41.7%) compared to patients with middle (12%) and upper (2.4%) level (*P*=0.001). Extension deformity rate was higher in patients with lower localization of fracture line according to olecranon fossa (33.3%), and flexion deformity rate was higher in patients with middle localization (12%) (*P*=0.001) (Table 1).

Eleven patients (9.9%) had BMI ≥25 and 14 cases (13.2%) had multidirectional instability. Fifty-four of distal fragment cases (44.3%) had posterior, 32 of them (26.2%) had posterolateral, and 36 of them (29.5%) had posteromedial localization. Nine cases (7.7%) had medial spike. There was no statistical significance between BMI, direction of distal fragment, medial spike presence and reduction type (*P*>0.05). There was a statistical relationship between multidirectional instability and open surgery rates (*P*=0.004).

There was no statistical significance between the surgeons performing the surgery and coronal (*P*=0.208) and sagittal (*P*=0.40) deformities. On the other hand, there were statistical differences between surgeons in terms of reduction type (*P*=0.009) and surgery duration (*P*=0.004).

DISCUSSION

Supracondylar humerus fractures are common fractures of childhood age, and primary treatment method in displaced fractures is closed reduction and pin fixation. Open reduction can be required in cases that cannot be treated with closed reduction[2]. In the literature, the topic of open reduction and acceptable reduction is not clear[6]. In our study, there was no statistical difference between fracture level according to olecranon fossa and open/closed reduction rate.

Sagittal plane flexion deformity was very high in cases where the fracture line passed through the middle level of olecranon. This may be due to the fact that it is difficult to ensure continuity of reduction

Table 1: Comparison of patients' characteristics according to olecranon fossa level

Patients' characteristics	Olecranon fossa level			*P*-values[1]
	Lower n (%)	Medium n (%)	Upper n (%)	
Sex				0.95
Boy	7 (58.3)	15 (60.0)	53 (62.4)	
Girl	5 (41.7)	10 (40.0)	32 (37.6)	
Reduction type				0.56
Open	3 (25.0)	6 (24.0)	29 (34.1)	
Closed	9 (75.0)	19 (76.0)	56 (65.9)	
Coronal plane deformity				<0.001
None	6 (50.0)	16 (64.0)	74 (87.0)	
Varus	5 (41.7)	3 (12.0)	2 (2.4)	
Valgus	1 (8.3)	6 (24.0)	9 (10.6)	
Sagittal plan deformity				0.001
None	8 (66.7)	20 (80.0)	80 (94.0)	
Extension	4 (33.3)	2 (8.0)	3 (3.6)	
Flexion	0 (0.0)	3 (12.0)	2 (2.4)	

[1]Chi-Square Test

during fixation in this middle area since it's very thin and there is a tendency for proximal fragment to move to posterior side due to gravitational force during surgery. The reason for this conclusion may be the result of the fact that front-rear diameter of distal humerus at middle level of olecranon fossa is an anatomically narrowed down area in the sagittal plane. The bone surface area in the axial plane is required to be aligned opposingly during closed reduction would be less. This condition may cause difficulties in closed reduction or problems in terms of ensuring continuity of the reduction achieved. Furthermore, soft tissue support by both capsule and collateral ligaments, and congruency of the elbow joint might make lower area more stable than the middle one.

Radiohumeral, radioulnar and humeroulnar joints comprising the elbow joint are surrounded by a single joint capsule. Elbow joint capsule includes olecranon, coronoid fossa and radial fossa. The tongue-cavity-like consistency of the humerus in radius and ulna has a structure making the shaft in lateral-medial axis almost anatomically impossible[5]. The fracture line passing through the lower level of olecranon fossa means a small distal part remaining inside the trochlear incisura of ulna. Postoperative coronal and/or sagittal deformities may occur as a result of the fact that manipulation of this distal part is difficult even in the case of open reduction. This is because it is embedded between coronoid process in the front and ulna in the rear and it has weak capsular connections.

A study has revealed that recognition of metaphysis-diaphysis fractures on olecranon fossa should be separately evaluated. It has been argued that the fractures on this level would affect surgery durations based on transverse or oblique extension of the fracture, or postoperative Bauman and lateral humero-capitellar angles[14]. Lim *et al* have stated that radiography images would provide warnings in terms of pre-surgery difficulties[15]. We think that determination of fracture line level according to olecranon fossa in preoperative radiographies would be beneficial in terms of predicting the possibility of challenges of closed reduction and postoperative coronal and/or plane deformity.

Acceptance tolerance of the surgeon in closed reductions and post-reduction risk consideration will affect open reduction rates[12]. The surgeon's belief in remodelling feature of pediatric fractures may affect postoperative malalignment rates[16]. Based on personal characteristics of the surgeon, the acceptance of the reduction obtained after closed reduction and their belief in bone remodelization might have affected the frequency of open reduction in our study. Furthermore, the surgical approach selected by the surgeon upon deciding on open reduction might have caused a difference between orthopedists in terms of surgery durations.

Jacob *et al* have stated that anatomical reduction of the fracture is not significant in pediatric age group and it has a minor effect on final joint ROM. It results in remodelization that will tolerate a wide range of malalignment[17]. On the other hand, Simanovsky *et al* have reported that 77% of patients with insufficiently reduced supracondylar fractures showed radiographic abnormality at skeletal maturity and 50% of them had limited elbow flexion[18]. It is clear that measured postoperative deformities will decrease by reshaping of the bone. It is another disadvantage of the study that the effect and significance of these measurements on elbow functions is unknown.

The purpose of the treatment of supracondylar humerus fractures is to achieve a reduction success

that is the closest to normal anatomy. Otherwise, non-cosmetic deformities which occur after treatment of displaced fractures that may cause restriction of movement might be inevitable[19]. Clinical value of radiographic examinations after surgical treatment of displaced supracondylar humerus fractures in pediatric patients is unknown[8]. The reliability of radiographic assessment was questioned due to relatively wide normal variation level in Baumann angle (almost 20°) and measurement errors in Baumann angle (up to 7°)[8]. Measurements outside a specific range of values were assessed as deformity in our study. Values measured outside normal values albeit not extremely high might be due to measurement errors or anatomical variation. In their study, Tuomilehto *et al* found an abnormal Baumann angle in almost one-third of elbows of patients who underwent surgery with supracondylar humerus fractures. However, none of them were subject to corrective osteotomy[8]. Disadvantage of determination of fracture line localization according to olecranon fossa is that it does not provide information about deformities related to clinical problems and osteotomy needs.

The limitations of our study were that it was a retrospective study and information on long-term functional or cosmetic deformities were insufficient. Even if open reduction or coronal deformities are included in statistical evaluations, we believe that more valuable data would be obtained by a prospective study with a long follow-up term standardizing effective factors and evaluating only the olecranon fossa level. Another limitation is that none of the patients had a fracture line passing through all three parts of circle of olecranon fossa in our study population. Since our classification system relies on the level of fracture line passing through the olecranon fossa, the involvement of all three parts of the circle may lead to distinctive and radiological clinical outcome.

CONCLUSION

Evaluation of fracture line level according to olecranon fossa in anteroposterior elbow radiographies of pediatric supracondylar fractures can provide preoperative information in terms of estimating the possibility of postoperative coronal plan deformity to the surgeon. This condition can be a factor to be evaluated in terms of prescribing cosmetic deformities that may occur in early postoperative period and informing patient's relatives about this fact.

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Author's contribution: Ali Yuce: idea conception, data collection, data analysis, results, discussion and literature review; Mustafa Yerli: idea conception, data analysis, results, discussion and literature review; Tahsin Olgun Bayraktar: data analysis, results, discussion and literature review; Yunus Imren: data analysis and results writing; Suleyman Semih Dedeoglu: data collection and literature review; Hakan Gurbuz: discussion and literature review.

Conflict of Interest: The authors declare that they have no conflict of interest.

Patients' consent: Written informed consents were obtained from all study participants.

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Original Article

Individualized nutritional support ameliorates protein-energy wasting in patients with maintenance hemodialysis: A single-center experience

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ABSTRACT

Objective: To evaluate the effect of individualized nutritional support on protein-energy malnutrition in patients with maintenance hemodialysis
Design: Retrospective study
Setting: Department of Nephrology, the Seventh Affiliated Hospital of Sun Yat-sen University
Subjects: Maintenance hemodialysis patients
Interventions: Patients with regular nutritional support received routine nursing and nutritional guidance, while patients with individualized nutritional support had personalized nursing plan with particular emphasis on proper protein intake and restrictions on sodium, potassium, calcium and phosphorus intake.
Main outcome measures: Patients' dietary behavior management scores, electrolyte levels and nutritional status indicators at three months post-nursing were compared.
Results: After nursing, the scores of self-care, liquid control, low-salt diet, low-potassium diet, and adherence in times of particular difficulty in patients with individualized nutritional support were significantly higher than those with regular nutritional support (P<0.001). Moreover, compared to patients with regular nursing, patients with individualized nutritional support had lower levels of serum calcium, phosphorus and potassium (P<0.001), and their nutrition status indicators, including triceps skinfold thickness, upper arm circumference, levels of albumin and hemoglobin were significantly improved (P<0.001).
Conclusion: These data demonstrate that individualized nutritional intervention can effectively regulate diet behaviors of patients, correct the water-electrolyte disorder, and ameliorate protein-energy wasting in patients with maintenance hemodialysis. Further clinical trials addressing long-term impacts of individualized nutrition intervention on patients with maintenance hemodialysis are warranted.

KEY WORDS: care, chronic kidney disease, individualized nutrition intervention, maintenance hemodialysis protein-energy wasting

INTRODUCTION

Chronic kidney disease (CKD) remains a global health and economic burden and is associated with a decline in quality of life and shortened life expectancy. According to the latest report, 697.5 million people worldwide were diagnosed with CKD in 2017, of which 1.2 million died and 3.1 million were on dialysis[1]. Maintenance hemodialysis is a blood purification therapy used to treat uremia in patients with end-stage kidney disease, the final stage of CKD[2]. While maintenance hemodialysis could effectively remove uremic toxins from the blood and control disease progression[3,4], the mortality rate among hemodialysis patients remains high due to various etiologies including protein-energy wasting (PEW)[4-6]. According to The International Society of Renal Nutrition and Metabolism, PEW refers to the decreased body protein mass and energy reserves caused by multiple

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Table 1: Baseline characteristics of patients with regular nutritional support or with individualized nutritional support

Parameters	Regular (n=25)	Individualized (n=25)	*P*-value
Age (year)	60.48±12.37	60.93±12.41	0.898
Gender (male/female)	15/10	14/11	0.774
Primary diseases			
Chronic glomerulonephritis	17	16	0.765
Diabetic nephropathy	8	9	
Weight (kg)	57.21±7.35	57.48±7.20	0.896
Amount of dehydration (kg)	1.94±0.30	1.92±0.31	0.818
Systolic pressure (mmHg)	113.27±3.51	113.40±3.58	0.897
Diastolic pressure (mmHg)	84.36±2.37	84.29±2.40	0.918
Educational levels			0.637
Primary school	9	8	
Middle school	8	9	
High school or technical secondary school	5	4	
Undergraduate or junior college	3	4	

factors, such as anemia, volume overload, nutrient loss during dialysis, and production of inflammatory cytokines[7,8]. Despite advances in CKD management, PEW frequently occurs in maintenance hemodialysis patients, with a reported incidence ranging from 28% to 52%[6,9-11], and is associated with significant increases in morbidity and mortality as reported by many centers[12-17]. Therefore, there is an unmet need to explore strategies for the prevention or treatment of PEW in patients with maintenance hemodialysis.

It has been reported that dietary patterns and behaviors may affect the nutritional status as evaluated by the Subjective Global Assessment and are related to all-cause mortality in dialysis patients[5,18]. Indeed, patients on maintenance dialysis frequently suffer from loss of appetite, anorexia and inflammation, which can lead to reduced dietary intake and increased nutrient loss. The consensus in the field of dietetic-nutritional therapy recommends that the diet of CKD patients should include modulation of protein and caloric intake, control of sodium and potassium intake, and reduction of phosphorus intake[19]. However, the success and safety of dietetic-nutritional management of CKD patients often rely on patient adherence, education, interdisciplinary cooperation and follow-up[19].

Individualized nutritional intervention is a new nutritional nursing model based on an individualized nursing concept. Several reports support that the intensive individualized nutrition intervention increases nutritional intakes, prevents therapy-associated weight loss, and improves long-term prognosis in cancer patients[20,21]. However, it remains unclear whether the individualized nutrition intervention could improve the dietetic-nutritional management and ameliorate PEW in CKD patients.

This study aimed to evaluate the effect of individualized nutrition intervention on patients with maintenance hemodialysis. We compared the clinical characteristics of 50 CKD patients on maintenance hemodialysis with regular nursing and nutritional guidance or with individualized nutritional support in our center. We hypothesized that individualized nutrition intervention could help improve the dietary behaviors of patients and prevent PEW during maintenance hemodialysis.

SUBJECTS AND METHODS

Subjects

Fifty patients who received maintenance hemodialysis from January 2019 to April 2020 in the Department of Nephrology at The Seventh Affiliated Hospital, Sun Yat-sen University were included. The inclusion criteria were as follows: (1) diagnosed with chronic renal failure; (2) receiving maintenance hemodialysis therapy for at least 3 months; (3) clear in consciousness to cooperate with the completion of the study; and (4) signing the informed consent. The exclusion criteria were as follows: (1) having mental disorders; (2) complicated with the malignant tumor or hematological diseases; and (3) loss of follow-up and dropping out of the study. Among these patients, 25 patients received regular nutritional support and 25 patients received individualized nutritional support. Their main characteristics including age, gender, weight, primary diseases, blood pressure and education levels were listed in Table 1.

This study was reviewed and approved by the Ethics Committee of The Seventh Affiliated Hospital, Sun Yat-sen University. All patients provided informed consent prior to the study. This study was conducted in accordance with the 1964 Helsinki Declaration.

Study design

For patients with regular nursing and nutritional support, we conducted routine health education,

informed patients and their families of notices during maintenance hemodialysis therapy, comforted patients, emphasized the importance of maintenance hemodialysis, carefully monitored patient's vital signs, and made good records every time the hemodialysis was performed.

The individualized nutrition support was based on routine nursing care plus additional personalized nutritional plan. More specifically, the individualized nutrition intervention group, formed by renal physicians, the chief nurses, nurses and dietitians, would develop an individualized nutritional intervention plan for patients according to each patient's condition and characteristics of maintenance hemodialysis therapy. The group emphasized the importance of nutrition intervention to the patients first, and then implemented the nutrition intervention regimens as listed below.

Liquid restrictions

During the period of maintenance hemodialysis therapy, the daily weight gain of patients should be controlled within 5% as far as possible. Too much water intake can lead to edema and weight gain, so daily drinking water should be strictly limited. The patients were educated about the water content of foods and reducing the proportion of foods that are rich in water. When feeling thirsty, the patients can contain a little water in the mouth or chew gum.

Dietary sodium salt restrictions

Daily sodium salt intake should be strictly controlled. Patients or their families should reduce the addition of salt, soy sauce and other condiments when cooking dishes, and avoid eating preserved foods as far as possible.

Dietary potassium restrictions

Explain the dangers of excessive potassium intake to patients and tabulate the potassium content of various foods. Avoid eating food high in potassium in the daily diet, especially fungus mushroom, oranges, red jujube and other foods with high potassium. When cooking, take the appropriate measures to remove potassium, such as cooking after soaking the vegetable root and stem slices or blanching vegetables briefly.

Dietary phosphorus restrictions

Explain the dangers of excessive phosphorus intake to patients and tabulate the phosphorus content of various foods. Pay attention to seafood, animal viscera, egg yolk and other foods with high phosphorus, which should be prohibited.

Adequate protein intake

Assure at least 1.2g/kg of protein intake every day and increase the proportion of high-protein food in their daily diet, like lean meat and milk.

Study measurements

We collected and compared the data of dietary behavior management score, electrolyte levels (serum calcium, phosphorus and potassium), and nutritional status index (triceps skinfold thickness, upper arm circumference, albumin and hemoglobin) of the two groups at three months post-nursing.

The dietary behavior management score system was modified from literature[22]. The dietary compliance scale for kidney diseases was used for evaluation, which included five areas: self-care, liquid control, low-salt diet, low-potassium diet and adherence in times of particular difficulty. The maximum score for each area was 100, and the score was proportional to dietary behavior compliance.

Table 2: The dietary behavior management scores of patients with regular nutritional support or with individualized nutritional support

Parameters	Timing	Regular (n=25)	Individualized (n=25)	*P*-value
Self-care	Pre-nursing	77.54±5.46	77.83±5.52	0.853
	Post-nursing	78.21±6.35	85.30±7.09	<0.05
	P-value	0.691	<0.001	
Liquid control	Pre-nursing	78.19±6.02	78.32±6.14	0.940
	Post-nursing	78.93±6.75	86.07±6.83	<0.05
	P-value	0.684	<0.001	
Low-salt diet	Pre-nursing	77.62±5.91	77.90±5.98	0.868
	Post-nursing	78.35±6.43	86.12±6.76	<0.001
	P-value	0.678	<0.001	
Low-potassium diet	Pre-nursing	76.38±5.48	76.47±5.56	0.954
	Post-nursing	77.24±6.30	85.09±6.45	<0.001
	P-value	0.609	<0.001	
Adherence in times of particular difficulty	Pre-nursing	77.46±5.13	77.68±5.27	0.882
	Post-nursing	77.90±6.29	85.78±6.92	<0.001
	P-value	0.788	<0.001	

Table 3: The electrolyte levels of patients with regular nutritional support or with individualized nutritional support

Parameters	Timing	Regular (n=25)	Individualized (n=25)	*P*-value
Serum calcium	Pre-nursing	2.58±0.72	2.53±0.75	0.811
	Post-nursing	2.45±0.69	1.87±0.43	<0.05
	P-value	0.518	<0.001	
Serum phosphorus	Pre-nursing	2.34±0.24	2.30±0.26	0.575
	Post-nursing	2.28±0.25	1.81±0.27	<0.001
	P-value	0.391	<0.001	
Serum potassium	Pre-nursing	6.17±0.94	6.14±0.95	0.911
	Post-nursing	6.02±0.91	4.78±0.64	<0.001
	P-value	0.569	<0.001	

Statistical analysis

All statistical analyses were performed using the SPSS 26.0 software. Counting data were analyzed using a $\chi 2$ test and measurement data were analyzed using the t-test. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline patient characteristics

As shown in Table 1, baseline patient characteristics such as age, gender, primary disease, blood pressure and education level were comparable between patients with regular nursing and patients with individualized nutritional support. In particular, the majority of the participants were about 60 years old with primary diseases including chronic glomerulonephritis and diabetic nephropathy.

Individualized nutritional support enhances patient's dietary adherence and behavior

To determine the effect of individualized nutrition support on patient's dietary adherence and behavior, data on dietary behavior management scoring tests based on the report by Rushe *et al* were compared pre and post-nursing among patients in the control group and the intervention group[22]. As shown in Table 2, before nursing, the two groups showed no significant difference in dietary behavior management scores on the items including self-care, liquid control, low-salt diet, low-potassium diet and adherence in times of particular difficulty ($P>0.05$). However, after nursing, the scores of various dietary behavior management items in the individualized nutritional support group were significantly higher than those before nursing, and the scores were higher than those of the regular nursing group ($P<0.001$). These results indicate that individualized nutrition support has a positive impact on patients' dietary adherence and behavior.

Individualized nutritional support improves patients' electrolyte balance

Electrolytes and fluid management are critical for patients with maintenance hemodialysis[23]. We then compared the levels of serum electrolytes including calcium, phosphorus and potassium between the two groups (Table 3). Before nursing, the two groups showed no significant difference in the electrolyte levels ($P>0.05$). However, after nursing, the levels of serum calcium, phosphorus and potassium in patients with individualized nutritional support were

Table 4: The nutritional status indicators of patients with regular nutritional support or with individualized nutritional support

Parameters	Timing	Regular (n=25)	Individualized (n=25)	*P*-value
Triceps skinfold thickness (mm)	Pre-nursing	6.67±1.20	6.70±1.23	0.931
	Post-nursing	6.80±1.45	8.39±1.57	<0.05
	P-value	0.731	<0.001	
Upper arm circumference (cm)	Pre-nursing	14.17±1.85	14.27±1.96	0.854
	Post-nursing	14.39±2.01	16.95±2.48	<0.001
	P-value	0.689	<0.001	
Albumin (g/L)	Pre-nursing	35.66±1.80	35.83±1.85	0.743
	Post-nursing	36.02±2.31	39.45±2.74	<0.001
	P-value	0.542	<0.001	
Hemoglobin (g/L)	Pre-nursing	104.15±1.72	104.31±1.76	0.747
	Post-nursing	104.52±2.39	108.74±3.50	<0.001
	P-value	0.533	<0.001	

significantly lower than those before nursing, and the levels of serum calcium, phosphorus and potassium were all lower than those in patients with regular nutritional support (P<0.001).

Individualized nutritional support ameliorates the nutrition status, low albumin and anemia of patients

Before nursing, there were no significant differences in triceps skinfold thickness, upper arm circumference and the levels of albumin and hemoglobin between the two groups (P>0.05). After nursing, the triceps skinfold thickness and upper arm circumference of patients with individualized nutritional support were significantly higher than those in patients with regular nutritional support or before nursing (P<0.001, Table 4). Moreover, the levels of albumin and hemoglobin of the intervention group were higher than those in patients with regular nutritional support (P<0.001). These results suggest that individualized nutritional support improves the nutrition status and anemia of patients with maintenance dialysis.

DISCUSSION

This retrospective study yielded several findings. First, after nursing, the scores of dietary behavior management (including self-care, liquid control, low-salt diet and low-potassium diet) had been improved in patients with individualized nutritional support, suggesting the benefit of individualized nutritional support on patient's compliance of dietary behaviors. Moreover, after nursing, the electrolyte imbalance, low albumin levels, muscle mass and anemia in patients with individualized nutritional support were also improved, suggesting that individualized nutritional intervention can improve the nutritional status of patients, correct the water-electrolyte imbalance, and reduce the risk of malnutrition.

Uremia frequently occurs in patients with end-stage kidney disease and is associated with a high risk of death[24]. Maintenance hemodialysis, by utilizing technologies such as adsorption and filtration for blood purification, can effectively remove toxin molecules, correct acid-base balance and reduce renal inflammation[25]. However, during treatment, patients often suffer from loss of appetite, irregular eating behaviors and malnutrition, which would dampen the efficacy of dialysis and promote disease progression[26]. Therefore, nursing with high quality is critically needed for improving life quality and the success of dialysis in CKD patients. This demand gives rise to the individualized nutritional intervention in the clinic.

At present, the routine nursing measure for CKD patients during maintenance hemodialysis could be too general and lack specificity. These nursing measures are often unsatisfactory for CKD patients, especially for the patient with risks of malnutrition. How to reduce the risk of malnutrition in CKD patients has been a critical nursing problem that needs to be solved. Given that malnutrition is often associated with dietary nutrition, individualized nutritional intervention could be a highly targeted specialized nursing model for reducing the risk of malnutrition.

It has been demonstrated that compared with routine nursing, nutritional intervention is more effective and specialized. Individualized nutritional intervention integrates with individualized nursing concepts and gives full consideration to the patients' differences and the actual demands while making a nursing plan. During the implementation of nursing measures, the actual nutritional needs of patients can be satisfied, which fully demonstrates the personalized and humanized nursing spirit[27]. In this study, patients with individualized nutritional support received personalized nutritional guidance in addition to routine nursing measures and imposed dietary restrictions on dietary liquid, sodium, potassium, and phosphorus intake based on the characteristics of the maintenance hemodialysis therapy. At the same time, we adjusted dietary proportion to ensure that the daily protein intake can meet the nutritional needs of the patients.

It should be noted that including the albumin level as a nutritional status maker has been controversial as the albumin level could increase in various scenarios including inflammation and infection[28,29]. However, there is also compelling evidence showing that low albumin is frequently seen in CKD patients with PEW[8,30]. In this study, we observed that post-individual nutritional support, the levels of albumin in patients with maintenance dialysis significantly increased, along with increased levels of hemoglobin[31], suggesting that the nutrition status could be ameliorated in these patients.

We acknowledge that several limitations should be noted in this study. First, the sample size in this study is relatively small; a multi-center study with a larger sample size may strengthen the power of the study. Second, the relatively short follow-up time (3 months) makes it difficult to determine the effect of individualized nutritional support on critical outcomes of the CKD patients, such as infection, cardiovascular events and mortality. Despite these limitations, this study strongly supports that individualized nutritional support could be beneficial for preventing PEW in patients with maintenance hemodialysis.

CONCLUSION

In summary, individualized nutritional support used in maintenance hemodialysis therapy can effectively regulate diet behaviors of patients, correct

the water-electrolyte disorder, ameliorate PEW and reduce the risk of malnutrition. Clinical trials are warranted to confirm its effect on long-term outcomes of patients with maintenance hemodialysis at risk of malnutrition.

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Original Article

Professionalism narratives of Kuwait's future physicians: Impact of the hidden curriculum

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ABSTRACT

Objectives: Medical students in Kuwait University are formally instructed in Western professional values before being exposed to the hidden curriculum's informal everyday learning experiences during clerkships. This study discovers the professional perceptions of Kuwait's medical students and impact of the hidden curriculum on such perceptions.

Design: (1) Thematic analysis of 249 written narratives obtained via an online survey; (2) thematic analysis of 259 verbal narratives transcribed from focus group interviews; (3) a questionnaire assessing professional attitudes via professional domains developed by the American Board of Internal Medicine (n=119).

Setting: Kuwait University

Subjects: Medical students in Kuwait University

Intervention: None

Main outcome measure: Thematic analysis

Results: Most students (88%) agree with Western professional norms, especially honesty with patients (79%) and improving access to care (67%). Narratives yielded 12 themes. The most frequent was manifesting respect in clinical interactions (60.1%), with subthemes including communication skills (66.79%), nondiscrimination (17.56%) and respecting patient privacy (14.12%). Other themes included principalism (18.26%), creating a welcoming environment (4.08%), capitalizing on teaching opportunities (3.9%), managing conflicts of interest (3.19%), improving quality of care (2.66%), punctuality (2.3%), adherence to hospital regulations (1.95%), honesty towards patients (1.06%), dressing appropriately (1.06%), confidentiality (0.87%), and teamwork (0.53%). Expatriates were involved in narratives regarding improving access to care (100%), nondiscrimination (45%), respecting patient privacy (71%) and informed consent (73%).

Conclusions: The hidden curriculum reinforced formally instructed Western professional values and introduced students to unique professional values and challenges specific to Kuwait's culture. The adoption of a professional competency framework specific to Kuwait into the faculty's formal curricula and healthcare system is warranted.

KEY WORDS: hidden curriculum, Kuwait, medical student, narratives, professionalism

INTRODUCTION

The Liaison Committee on Medical Education mandates professionalism in medical education in the accreditation of medical schools worldwide[1]. After all, a physician's professional identity starts to develop during medical school[2].

Kuwait University's Faculty of Medicine, the only medical school in Kuwait, provides a seven-year long undergraduate medical education to an annual incoming class of 105 students, most of which are women (>75%) and Kuwaiti nationals (99.5%). The first four years are preclinical years, while the last three are spent in clerkships. Throughout their preclinical and clinical years, medical students are formally taught and tested on Western values of professionalism as defined by the American Board of Internal Medicine's Charter, including the following: just distribution, honesty and confidentiality[3]. Every year, they are

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instructed these values via the formal curriculum such as through didactic lectures, workshops, problem-based learning sessions, bedside teaching sessions during clerkships, and Objective Structured Clinical Examination (OSCE) stations. They are evaluated on punctuality, attendance, communication skills with patients and peers, and appropriate attire. In each OSCE, there are specific stations that assess student's communication skills in scenarios like breaking bad news, counseling patients, dealing with angry patients and managing conflicts with a colleague.

During clerkships, medical students indirectly pick up and learn professional values via their informal everyday learning experiences, and hence, the hidden curriculum. The hidden curriculum is defined as learning that occurs by means of informal interactions among students, faculty, and others and/or learning that occurs through organizational, structural and cultural influences intrinsic to training institutions[4]. It exists within each student's past learning experiences[4]. Role models have shown to be key players in the hidden curriculum, as students learn via observing their clinical tutors' interactions with patients, colleagues and/or students. Several studies suggested that the hidden curriculum has a more powerful impact on professional identity formation than the formal curriculum[4-6]. Other studies found the formal and hidden curricula to be equally vital, synergistically working together[7].

The hidden curriculum in Kuwait's hospitals might expose medical students to professional values that differ from the Western values they are taught through the formal curriculum. After all, professionalism is a social construct that varies across cultures[2,8]. Some attitudes and behaviors may vary in terms of acceptability depending on an individual's cultural background. For example, the Arabian professional competency framework supports professional autonomy, rather than patient autonomy, due to a depicted power balance between doctors and patients in Middle Eastern societies[9]. In Pakistan, a paternalistic model of patient care is implemented in which informed consent and confidentiality is not widely practiced[10]. In Uganda, the cultural Ubuntu philosophy, which defines collectivism, allows relatives of patients to have access to patient information and make medical decisions[11]. In Japan, it is considered unacceptable for doctors to question and speak up in front of senior doctors[12]. Thus, what may be deemed culturally appropriate professionally in Kuwait's hospitals might not be in the West. Moreover, physicians in Kuwait might face cultural-based professional dilemmas that might not exist in the West.

In light of the cultural discrepancy of professionalism, medical educators in Saudi Arabia have developed and instruct medical students with their own professional competency framework, Saudi-MEDS[13]. There has not yet been a consensus that defines the professional values and expectations of physicians and medical students in Kuwait.

In addition, there are rarely any studies on professionalism education in Kuwait. This study aims to gain insight on the professional perceptions of medical students in Kuwait and the impact of the hidden curriculum on such perceptions. We also hope to understand the perceived everyday learning experiences of Kuwait's medical students.

MATERIALS AND METHODS

Ethical approval was granted from Kuwait University Health Sciences Center's ethics committee. Data was then collected through three methods: a paper-based questionnaire, online survey and semi-structured focus group interviews. Students provided consent prior to the participation in each of the three methods.

A thematic analysis was conducted on two sets of data: written narratives and verbal narratives attained via the online survey and focus group interviews, respectively, from clinical year medical students in Kuwait University.

Questionnaire

A paper-based questionnaire was distributed to assess students' attitudes and behavior towards professional norms, as defined by the American Board of Internal Medicine (ABIM, 2002). These professional domains include principles regarding just distribution, honesty with patients, improving access to care, maintaining appropriate relationships with patients, maintaining professional competence, maintaining trust by managing conflicts of interests, protecting patient confidentiality, and fulfilling professional responsibilities, including self-regulation.

The questionnaire consisted of 14 questions, derived and based on a questionnaire developed by Campbell *et al*[14]. Six questions assessed students' level of agreement with professional norms of just distribution, honesty with patients, maintaining appropriate relationships with patients and relevant reporting. Four other questions, three of which are based on given clinical vignettes, assessed how students would respond in certain situations regarding just distribution, honesty with patients and managing conflicts of interest. In addition, three questions assessed whether students have broken patient confidentiality, feel prepared to maintain professional competence, and have reported unprofessionalism and medical errors.

The paper-based questionnaire was distributed to a stratified convenience sample of medical students

Table 1: The guide used for conducting focus group discussion.

Lead question	Probes
What does professionalism mean to you?	• What do you believe has contributed to your understanding of professionalism? • Tell us more about that.
Please tell us any specific professional and unprofessional experience/story you encountered in clerkships, and what that taught you about professionalism.	• How has this experience impacted you and your understanding of professionalism? • How did this experience make you feel? • What did you learn from this experience? • If the story involved witnessing an unprofessional action: did you report this incidence? Why or why not?
Do you believe there are barriers to reporting witnessed lapses of professionalism?	• What are these barriers? • How do you believe we can overcome such barriers?
How do you think we can improve professionalism in Kuwait's hospitals?	

in Kuwait University's Faculty of Medicine. A total number of 193 students completed the questionnaire (42, 47, 52, 37 and 15 students in their third, fourth, fifth, sixth and seventh academic year of study, respectively).

Focus group interviews

Semi-structured focus group interviews were conducted. The interviewers were all co-authors of this study (Eliwa, J; Albeloushi A; Alashqar A; Alkanderi M), trained medical students who were considered 'unbiased' because they held no formal teaching or administrative roles in the faculty[15]. At least two interviewers were involved in each session. Students were invited via convenience sampling. Inclusion criteria consisted of being a clinical year student (academic years 5-7).

A total of 7-9 clinical year students participated per interview, yielding a total sample size of 37. The interviews were held in a nonthreatening atmosphere within a comfortable venue in the faculty. Each interview lasted about 2-3 hours and was recorded and transcribed verbatim. Participants provided verbal consent and were ensured that their involvement in the study was voluntary, anonymous and would not impact their academic standing.

A structure for the focus group discussion's lead questions was prepared and vetted by the research team (Table 1). Medical students were asked to verbally describe what professionalism means to them. Moreover, they were asked to provide us with verbal narratives: to verbally describe any specific professional and unprofessional experience/story they have encountered in clerkships, and the professional insight they gained from each experience. Each student was allowed to narrate as many experiences as he/she wanted.

The interviews were held until thematic saturation occurred and a redundancy in responses was noted. By then, a total of 5 interviews were conducted, yielding a total of 228 verbal narratives for thematic analysis.

Online survey

An online survey (Table 2) was sent to each of the 305 clinical year medical students in the faculty with a participating sample size of 137. The survey was sent via WhatsApp mobile messaging application.

Each student provided written consent. The online survey collected each student's socio-demographic data, which consisted of gender, nationality and year of study. Students were then asked to provide written narratives: to describe any specific professional and

Table 2: Online survey questions

1. Sociodemographics:
    1. What is your year of study?
    2. What is your gender?
    3. What is your nationality?

Narratives

1. Please describe any specific professional experience/story you encountered in clerkships, and what that taught you about professionalism.
2. Please describe any specific unprofessional experience/story you encountered in
3. clerkships, and what that taught you about professionalism.

unprofessional situation they have experienced within clerkships and the professional insight they gained from each experience.

A total of 249 written narratives, 121 reflecting professional situations and 128 reflecting unprofessional situations, were attained for thematic analysis.

Thematic analysis

A thematic, qualitative analysis was then conducted on a total of 477 narratives (228 verbal, 249 written) following the process carried out and described by Karnieli-Miller *et al*[16]. First, a contextual descriptive analysis was conducted, followed by a thematic content analysis utilizing an immersion/crystallization method. Four of the coauthors (Eliwa, J; Albeloushi A; Alashqar A; Alkanderi M, Osman A) served as primary coders and developers of the coding scheme, while independently and collectively reviewing each coded narrative to ensure internal interpretation validity. Themes and subthemes were categorized according to content, frequency and extensiveness. Any discrepancies in categorization were sorted out by discussion.

Table 3: Sociodemographic characteristics of study sample (Focus Group Study)

Focus Group Study		
Characteristic	**n**	**Percent**
Year of Study		
5th	14	38
6th	13	35
7th	10	27

RESULTS

Sociodemographic

Each methodological approach yielded a representative sample in terms of gender and nationality (Tables 3-5). Students in each academic clinical year of study were represented in the online survey and focus group samples. However, final year medical students were underrepresented in the sample of students who participated in the questionnaire.

Questionnaire

Results are presented in Tables 6-7.

Narratives

Context

Some narratives expressed more than one theme. Thus, a total of 563 themes were expressed: 284 themes from 228 verbal narratives and 279 themes from 249 written narratives.

Table 4: Sociodemographic characteristics of study sample (Questionnaire)

Questionnaire		
Characteristic	**n**	**Percent**
Gender		
Female	115	60
Male	78	40
Year of Study		
3rd	42	22
4th	47	24
5th	52	27
6th	37	19
7th	15	8

Most of the narratives involved experiences held in the inpatient hospital setting, while 40% involved experiences that took place in the outpatient setting. About 20% of stories did not include any particular setting. Most stories involved patients and clinical tutors. Some stories included family members, junior doctors, other students and nurses. A majority of narratives included the explicit description of emotions (75%). About 10% of stories could not be analyzed due to lack of significant content.

Content

A majority of stories were "negative", describing unprofessional behaviors witnessed in clerkships, while the remaining stories were "positive", describing professional behaviors witnessed.

Thematic analysis yielded a total of 12 themes with some subthemes (Table 8). Each theme included both negative and positive stories. There was no difference in the frequency of themes reported according to gender and academic year of study.

The most frequent main themes are as follows: manifesting respect in clinical interactions (60.1%) and principalism (18.26%). Other themes included: creating a welcoming environment (4.08%), capitalizing on teaching opportunities (3.9%), managing conflicts of interest (3.19%), improving quality of care (2.66%), punctuality (2.3%), adherence to hospital regulations (1.95%), honesty towards patients (1.06%), dressing

Table 5: Sociodemographic characteristics of study sample (Online Survey)

Online Survey		
Characteristic	**n**	**Percent**
Gender		
Female	100	73
Male	37	27
Year of Study		
5th	39	29
6th	29	21
7th	69	50

Tables 6: Professional behaviors of respondents to the paper-based questionnaire

Professional Behaviors	
Domain	**Percentage of respondents (%)**
Just distribution of infinite resources Scenario: An otherwise healthy, long-term patient presents with his first episode of low back pain, lasting 2 days, with onset following some work around the house. He has no neuromuscular signs or symptoms. You explain to him that his symptoms will likely resolve with rest and analgesia and that you don't think any further investigation is warranted at this stage. However, the patient is convinced that he has a herniated disc and is quite insistent that he should have an MRI scan. Would you... 1. Order the MRI, 2. Order the MRI scan, but say that you are doing so reluctantly, 3. Refuse to order the MRI scan at this time.	58% answered 1 or 2
Honesty with patients As a doctor, would you tell a patient's family member something about a medical issue that wasn't true?	95% answered "No"
As a doctor, would you withhold information that a patient or a patient's family should have known about a medical issue?	84% answered "No"
Improving access to care Scenario: A foreign patient was admitted under your care complaining of sudden onset headache associated with nausea, vomiting, and seizures. An urgent CT scan revealed a space-occupying lesion for further work up with MRI brain. To proceed for an MRI, the patient needs to pay 90 KD, but his monthly salary does not exceed 60 KD. You contacted social services for help, but they were unable to offer financial assistance. The doctor decides to pay for the MRI out of his/her own pocket. Is the doctor's conduct professional?	54% answered "Yes"
Maintaining professional competence Please rate the extent to which you feel prepared to critically evaluate new clinical knowledge.	66% answered "Very Prepared" or "Somewhat Prepared"
Protecting patient confidentiality Have you inappropriately revealed information about a patient?	17% answered "Yes"
Maintaining trust by managing conflicts of interest Scenario: You and your partners have invested in a local imaging facility near your suburban practice. When referring patients for imaging studies, would you . . . 1. Refer your patients to this facility? 2. Refer your patients to this facility and inform patients of your investment? 3. Refer patients to another facility?	20% selected 1, 68% selected 2
Would you refer a patient to your own private clinic?	88% answered "Yes"
Fulfilling professional responsibilities, including self regulation Have you had direct personal knowledge of a physician who was impaired or incompetent in your hospital, group, or practice?	44% answered "Yes"
If yes, did you ever report that physician to a hospital, clinic, professional society, or other relevant authority?	70% answered "Never"

appropriately (1.06%), confidentiality (0.87%), and teamwork (0.53%).

Manifesting respect

The most frequent theme was manifesting respect in clinical interactions with patients, colleagues and medical students. Patients were involved in most narratives involving this theme (69%). Its main subthemes included communication skills (66.79%), lack of discrimination (17.56%) and respecting patient privacy (14.12%).

Students took note of how physicians communicate with patients. They appreciated doctors who greeted patients, actively listened to them, showed empathy, spent time with patients, provided full disclosure, addressed patient's needs and questions, handled difficult conversations and difficult patients, and utilized an appropriate choice of language and use of humor. They also expected doctors to communicate the same way with patients' family members. Doctors who communicated well inspired them and were described as "good doctors". They recognized communication skills as a way to build rapport and trust with patients. They also noted the negative consequences of communicating poorly with patients, including having patients feel hurt, uncomfortable, inclined to share less information, and the desire to change physicians.

"There's a doctor who is very professional. For every patient that comes in, the doctor gets up, calls their name, welcomes them in, and says hi to them. He treats each

Tables 7: Attitudes of respondents to the paper-based questionnaire

Attitudes towards Professionalism	
Domain	**Respondents who agree (%)**
Just distribution of finite resources Physicians should minimize disparities in care due to patient race or gender.	89
Honesty with patients Physicians should disclose all significant medical errors to affected patients and/or guardians.	73
Fulfilling professional responsibilities, including self-regulation All instances of significantly impaired or incompetent colleagues should be reported to hospital, clinic, or other relevant authorities. All observed significant medical errors should be reported to the hospital, clinic, or relevant authorities.	74
Maintaining appropriate relationships with patients Please rate the appropriateness of emotional relationships between adult patients and physicians.	20

patient with the same respect and courtesy. He inspired me to become just like him."

"And the doctor managed to deliver the bad news to her in a very professional and polite way. I really liked the way he treated the patient. He explained to her everything she needed to know in a simplified way. And he was able to calm her down when she was crying. I hope that one day I'll be a good doctor like him. "

Students described showing empathy as a form of professional communication skills. They also recognized the power of empathy in gaining a patient's trust, and thus, adherence to management. Through their narratives, students' very own sense of empathy and emotional responsibility towards patients can be felt. The following narratives are such an example:

"In the ICU, a patient was very aggressive and agitated, he was refusing medical treatment. The doctor in charge very calmly explained everything and showed him empathy, which caused the patient to change his mind and accept treatment."

"Doctors were talking about an unconscious patient. Cardiologists and internists were discussing whether to give an unconscious patient certain medications. The medications will benefit his cardiovascular system but damage the rest of his body. The internist said, 'it's better to just let him die', and the patient's relatives heard. I couldn't speak up about it. There wasn't any humanity in the situation on the internist's side. The internist wasn't professional and treated the patient like a machine."

Students also expected physicians to show respect not only in front of patients, but in their absence as well. To students, it was unjustified for a doctor to be disrespectful. The following narrative is an example:

"Surgeons say bad words behind a patient's back. Even if the patient is sedated, they shouldn't say that. There's no excuse no matter how stressful your career or educational journey is, you need to have respect and self-control."

Respecting patients includes treating patients equally, without a discriminatory attitude based on their nationality and socioeconomic status. Half of the stories involving lack of discrimination involved expatriates. Expats were also mainly involved in narratives including respecting patient autonomy (70%), informed consent (70%) and justice (100%). Students recognized expats (who make up 60% of Kuwait's population) as a vulnerable population in Kuwait's hospitals who are more susceptible to being treated unprofessionally. They reported that expats are more likely to be disrespected with poorer communication skills and less regard for their privacy and informed consent. Students sympathized with expats being mistreated, feeling disappointed towards doctors who did so. Furthermore, they felt motivated to always treat patients of all backgrounds equally.

"If a Kuwaiti says 'no' to being examined by medical students, the doctors respect his wishes and leave him alone. If a non-Kuwaiti says 'no,' they pressure them more and guilt them into saying 'yes'. It's basically as if they don't have a choice, but they do."

"One of the internal medicine doctors placed her left foot on the patient's bed without any respect to him while giving me a session. It probably happened because the patient was not Kuwaiti. There is a difference in the way they deal with patients in terms of nationality. It's so annoying to see such an attitude in this profession."

Students appreciated moments of respecting patient privacy, including being welcomed into a patient's room prior to entering and protecting patients from any unnecessary physical exposure. They felt it developed a sense of trust, respect and safety between the patient and doctor.

"When rounding on patients kept in a general (not private) room, I saw multiple doctors and students who do

Table 8: Results of thematic analysis of verbal and written narratives

Professional Themes Derived from Clinical-Year Kuwait University Medical Students' Narrative Reflections	
Themes & subthemes	**Frequency (%)**
Manifesting respect towards patients, medical students, and colleagues (including junior doctors, doctors in other specialties, and nurses)	60.1
Communication skills with patients	
Active listening	
Addressing questions and needs	
Appropriate choice of language and use of humor	
Dealing with difficult patients	
Disclosure of information	
Greeting the patient	
Handling difficult situations/conversations with patients and/or their families	
Minimizing persona cellphone use	
Non-judgemental attitude	
Showing empathy	
Spending time with patients	
Nondiscrimination	
Based on appearance	
Based on gender/encouraging females to pursue all specialties	
Based on Kuwaiti heritage	
Based on nationality	
Based on socioeconomic status	
Respecting patient privacy	
Avoiding unnecessary exposure during physical examination	
Acting respectfully to patients and families in challenging situations	
Being tolerant to mistakes, providing constructive feedback to juniors	
Establishing and maintaining relationships with patients	
Principalism	18.26
Patient autonomy	
Informed consent for clinical and teaching purposes	
Justice (Improving access to care)	
Personally financing patient's expenses	
Non- maleficence	
Beneficence	
Creating a welcoming teaching environment	4.08
Respecting students	
Being tolerant to mistakes, providing constructive feedback and evaluation	
Including and acknowledging medical students	
Nonjudgmental environment	
Friendly attitude towards students/caring for students	
Capitalizing on teaching opportunities	3.9
Active teaching	
Receptive to questions	
Using opportunities to teach values and manners	
Clear expectations towards students	
Managing conflicts of interest	3.19
Referrals to private clinic	
Self-marketing via social media	
Receiving gifts from patients	
Improving quality of care	2.66
Punctuality	2.3
Adherence to hospital regulations	1.95
Honesty towards patients	1.06
Dressing appropriately	1.06
Confidentiality	0.87
Teamwork	0.53

not start an examination or their conversation unless they make sure that the curtain is closed and speak with a lower voice to keep their conversation somewhat private."

"In urology rounds, the doctor in charge went into the patient's room without knocking on the door and uncovered the patient, who was around 18-20 years of age, and exposed his groin area to check up on a urethroplasty. The patient was asleep while all of this happened! What if the patient's mother was inside without her scarf on? There was no respect to the patient's dignity/privacy."

Students also reported the vitality of respecting colleagues, including nurses, junior doctors and medical students. They noticed the hierarchy that lies within each team and how conflicts that arise between doctors are handled. Professional handling of conflicts between doctors included constructive criticism, dealing with conflicts privately and avoiding gossip.

"Surgeons get very upset and yell at a nurse if she is one second late in handing over an instrument. It's not professional. Nurses are human."

Principalism

The second major theme was principalism, including respecting patient autonomy and informed consent (78%), improving access to care (11.4%), beneficence (6.6%), and non-maleficence (3.8%). Most stories involving informed consent were directed for teaching purposes, such as bedside teaching and conducting physical examinations. Students admired doctors who took informed consent for teaching purposes even if it came at the expense of their own clinical exposure. They expressed guilt and embarrassment when being instructed to examine a patient without permission. They also recognized that the consent of non-Kuwaiti patients had less weight, and hence the potential to be taken into less consideration, than Kuwaiti patients. Other stories revolved around the importance of taking permission prior to sharing patient information, including photographs, on social media for education purposes.

"In front of 13 people in a room, a successful doctor told a mentally disabled patient's family that we [medical students] will examine the patient and give her money in return. It was obvious that they are in need, but she couldn't even reply because of how embarrassed she was. He then exposed the patient without her permission and started taking pictures of her condition (tuberous sclerosis) without permission. He asked the patient's sister if we could take a picture of her face and cover her eyes, but before she could reply, he told a student to take a picture. If she was Kuwaiti, he would never have done that."

"Once we had a patient in the OPD with breast discharge. The patient refused students to examine her because she was embarrassed. The doctor got upset and pressured the patient to be examined by students, even though the patient refused twice."

All the narratives regarding improving access to care involved expats and whether personally financing the healthcare costs of expats in need was considered professional or not. Some students considered it professional, even if it meant violating hospital regulations, while others did not.

"After a patient was discharged, the doctor took his hand and walked him out of the ward and told him not to pay. He had a debt of more than 1,800 KD. I think this is professional even if it is against the hospital's rule."

Medical education themes

The third and fourth most common themes were creating a welcoming environment and capitalizing on teaching opportunities. Students believed clinical tutors act professionally when they treat students with respect, include and acknowledge students as part of the team, actively teach, use opportunities to teach values, are receptive to questions, and provide constructive feedback in a positive manner while being tolerant to mistakes. Students felt respected when they were respected and treated as colleagues, especially in front of patients. They also felt receiving special treatment based on their nationality, heritage and gender was inappropriate. Several female students reported feeling discouraged into pursuing male-dominated specialties such as surgery by tutors who barely knew them, merely based on their gender, rather than their merit. They highly appreciated and were inspired by tutors who created a positive teaching environment.

"The professional way of dealing with a student is if you want to ask me a question about a case, do so outside of the room, not in front of the patient. Also, if I say something wrong, you don't have to make a big deal about it- just tell me to go read about it more and ask me about it tomorrow. Don't be rude to me. I respect people who don't talk to us rudely in front of patients."

"I loved my pediatrics rotation because I ask tutors questions. Anything I don't understand, I ask about, and they answer my questions. It was amazing- a positive environment. Once, I felt like I benefited so much that I wanted to give my tutors a flower."

"A doctor walked into a PBL session full all female students. He said, 'Oh you're all females, so it looks like we'll have a lot of family medicine physicians.' Many of us got hurt by that."

Managing conflicts of interest

Narratives involving managing conflicts of interest involved various opinions on only two topics: the professionalism of accepting gifts from patients and transferring patients in the public sector to one's own private clinic. Most students believed it was culturally appropriate to receive gifts and considered refusing

gifts as a sign of disrespect. Some students believed it was a conflict of interest to refer patients to your private clinic while others did not.

"Of course, I would accept a gift from a patient. As long as it's not a bribe, it would be rude not to accept."

"The doctor should inform a patient of the benefits of both private and public clinics, and let the patient decide what s/he wants."

"If a patient really needs private clinic, the doctor should recommend any clinic, not his own."

Other results

Students reported facing several barriers to reporting lapses of professionalism carried out by their clinical tutors. These barriers included a lack of reporting system, jeopardizing relationships with their future colleagues, and receiving negative evaluations from reported tutors. Only a single student ever reported a lapse of professionalism conducted by a tutor because she felt safe to do so, as evident in the following narrative.

"I think it's the way you speak up when addressing a doctor who has done something unprofessional that matters. I once spoke up to a professor. I noticed he wasn't washing his hands. Other students told me it's okay, but I felt it was right for me to speak up. I didn't want to embarrass the doctor, so I wrote a comment on a paper that I handed over to him. He looked at the paper and smiled. In the paper, I wrote: 'Dear doctor, you are a role model to all of us, but hand washing is one of the rules of patient safety.' I didn't write my name to avoid embarrassment. I am very satisfied that I spoke up. I think I spoke up because I knew he is a good doctor with a good personality."

Throughout their narratives, students suggested solutions to several professional issues they witnessed. Some of these suggestions include: providing informed consent in a patient's native language to ensure that patients have full disclosure of information, being more empathetic towards a patient's condition by discussing his/her case privately in another space, developing a system that holds doctors accountable for being disrespectful without providing social consequences to the reporter, providing counseling sessions to doctors to develop their communication skills.

"We need to change the mindset of the doctors here. These changes take time and should be implemented now, not when we become consultants. Change doesn't happen overnight."

"Doctors should have counseling services available to them, so they don't project anger towards people."

When questioned on the upbringing of professionalism, different opinions arose. Some suggested it was an internal part of one's nature and not something that can be taught. Others believed it resulted from one's environment, and hence, is subject to habituation.

"I think professionalism depends on the working environment you are exposed to. If the whole hospital is unprofessional, then the professional becomes unprofessional."

"I don't get as shocked or affected when I witness unprofessional behavior because I've gotten used to it. But I will never become unprofessional- it's impossible. One of the reasons I entered med school was because I witnessed unprofessional behavior of doctors, and I was inspired to be the opposite of them. I believe that professionalism comes all the way down to how a person was raised. I think the environment may have an effect, only if the doctor allows it to."

DISCUSSION

The hidden curriculum not only reinforced and strengthened professional Western values that were instructed via the formal curriculum, but also introduced students to professional values and challenges that are specific and unique to Kuwait's culture.

Kuwait's medical students recognize and agree with most Western professional values. However, two key values were never mentioned in narratives: continuing professional development and relevant reporting. The lack of understanding the professionalism behind relevant reporting might contribute to the barriers that prevented most students from reporting or planning to report a lapse of professionalism. It's been shown that most final year Faculty of Medicine students at Kuwait University did not even know where to file a report[17].

Similar to other studies, punctuality and dressing appropriately were professional themes[17]. The weight given to those values might derive from the disciplinary consequences that students in the faculty may face, including repeating an academic year, if they don't abide by them[17].

The emphasis on respect is consistent with various studies[17-19]. Disrespecting a patient equated to dehumanization, which antagonizes the humanitarianism that drew students to choose medicine as a career. Lack of social discrimination emerged as a professional value in our study, something we did not find in other similar studies. They attributed the vulnerability of expats to the healthcare culture that lies uniquely within Kuwait. In the eyes of Kuwait's collectivist society, a national is an extension of his/her family, and hence, disrespecting a Kuwaiti patient comes with social consequences and accountability. Although expats make up 60% of Kuwait's population, they are individuals who do not assimilate into Kuwaiti culture. Hence, disrespecting an expat doesn't yield any social accountability. Furthermore, Kuwait's healthcare system institutionalizes discrimination. For example, Kuwaitis are provided free public healthcare

whereas expats have to finance their own healthcare expenses. Certain medications and certain hospitals are only accessible to nationals, not expats. In light of such culture, doctors who treated patients with equal respect were looked up to, serving as positive role models and inspiring students to do the same in the future.

The hidden curriculum introduced students to "gray areas", professional dilemmas that are unique to their culture and society. For example, students often came across expats who could not finance their healthcare fees for certain diagnostic and therapeutic procedures. To some students, improving access to care meant paying patient's fees from their own pockets, even if it meant violating hospital regulations. After all, conducting daily charitable actions is a pillar of Islam. To other students, Western values of patient/physician barriers and respecting hospital regulations, took precedence. Moreover, most students believed it was professional to accept gifts from patients, even if it contrasted with Western values. They perceived it as a sign of respect. Turning a gift away from anyone, even if you don't want it, is considered disrespectful in Islamic faith. The professionalism of accepting gifts from patients was similarly found among Estonian doctors[20]. Moreover, Kuwaiti doctors are legally allowed to simultaneously work in the public sector on a fixed salary and private sector on a fee-for-service incentive. This is not common in the West, and hence, students were not formally instructed on whether it is professional or not to refer patients from your public to private clinic. As a result, a discrepancy in opinions existed regarding the professional dilemma.

Our results show that professional frameworks developed in other Islamic, Arabian countries might not be applicable to Kuwait. Spirituality and faith was not mentioned as a compass or foundation of professionalism as it is the United Arab Emirate's framework[21]. Humility and a "god-fearing nature" were not reported as they were by Saudi Arabian students[22]. Despite living in a collectivist society, students did not prioritize a patient's family's needs above the patient's own[21]. Moreover, students upheld patient autonomy rather than the professional autonomy preached by the Arabian framework[9]. Moreover, the Arabian framework was drafted by a team of representative educators from around the Arab region, except Kuwait.

Students learned what professionalism means to them by internalizing and analyzing their everyday experiences in clinical settings, especially by analyzing and questioning the actions and attitudes of their clinical tutors[6]. Even on social media, how clinical tutors act has an impact. For example, one student noted witnessing two clinical tutors quarrel on social media taught her how to communicate professionally, privately with colleagues during a difference in opinions.

Similar to other studies, the majority of reported experiences were negative[4,23]. This is likely because people develop a more powerful emotional response and hence, a more easily retrievable emotional memory, from negative experiences[24]. We have to invest in the vital role of clinical tutors in order to empower and strengthen the professionalism of medical students, as well as guide them on how to navigate through various professional dilemmas they may face in the future, especially cultural ones[6]. This investment comes in the form of enforced professional faculty development (via regularly held workshops and training sessions) and the regular, anonymous evaluation of faculty professionalism by medical students (via standardized forms and reflective narratives).

The formal curriculum provided students with a strong foundation on what it means to be professional based on a Western context. Thus, whenever students felt professionally conflicted in clinical settings, they could turn to and question their formal lessons. The formal curriculum will provide an even greater asset to students if it integrates within it a more local approach: addressing professional situations and values that are specific to Kuwait's culture. Thus, developing a professional competency framework that is specific to Kuwait, along with the adoption of such framework into the curricula and healthcare system is warranted. Moreover, we recommend the development of a reporting system, where physicians and medical students feel safe reporting lapses of professionalism and holding others accountable.

CONCLUSION

As in other parts of the world, the specific culture in Kuwait introduced unique professional challenges. The formal curriculum taught in Kuwait University based on Western professional values did not address those unique challenges and students were only exposed to them through the hidden curriculum. Consideration should be given to amending the formal curriculum in Kuwait to address those specific issues.

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Original Article

Swinging thyroid function: A difficult task in clinical practice

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ABSTRACT

Objectives: Autoimmune thyroid disease (AITD) encompasses several conditions, such as autoimmune Hashimoto's thyroiditis (HT) and Graves' disease (GD). Switching from one thyroid functional status to another has been relatively seldom reported. The aim of the study was to report the evolution of ten cases of AITD with oscillating thyroid function.
Design: Observational study
Setting: Department of Endocrinology, Emergency County Hospital, Timisoara, Romania
Subjects: Ten patients with AITD with fluctuating thyroid function
Intervention: The patients were actively monitored; their laboratory, clinical data and treatment have been recorded.
Main outcome measures: The initial type of AITD, the severity and the duration until each phase of hypo- or hyperthyroidism occurred, the correlation with autoimmune parameters, and the effect of each type of treatment were evaluated.
Results: All patients were monitored and treated according to thyroid functionality. Five patients were initially diagnosed with GD and treated with antithyroid drugs. After a variable period of time (3-24 months), they developed autoimmune hypothyroidism. Three patients presenting at diagnosis with HT developed autoimmune hyperthyroidism after a significantly longer time. Two patients displayed repeatedly fluctuating thyroid function during the time, with a succession of different functional aspects (hypo-hyper and vice versa).
Conclusions: The oscillating clinical thyroid status of the reported cases may reflect the balance between stimulating TSH receptor antibodies and blocking TSH receptor antibodies, which can be influenced by many factors. These AITD cases require regular clinical follow up and frequent laboratory testing to detect and treat the new thyroid functional status as soon as possible.

KEY WORDS: autoimmune thyroiditis, hyperthyroidism, hypothyroidism, thyroid autoantibodies

INTRODUCTION

Autoimmune thyroid disease (AITD) is the most prevalent organ-specific autoimmune disorder, affecting 2-5% of the general population. However, the incidence of humoral thyroid autoimmunity, without clinical disease, seems to be much higher. Classically, AITD encompasses a spectrum of conditions, ranging from Hashimoto's hypothyroidism at one end to Graves' hyperthyroidism at the other. Recent views consider the hypothesis of a possible continuum between Graves' disease (GD) and Hashimoto's thyroiditis (HT)[1]. The major AITD entities (GD, HT) share many common characteristics: aggregation in same families and occurrence of both entities in monozygotic twins, lymphocytic infiltration of thyroid parenchyma (with reactive B and T lymphocytes), occurrence (synchronously, sequentially) in the same thyroid gland, involvement of similar antigens and antibodies, etc[1].

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The thyroid-stimulating hormone receptor (TSH-R) is the major autoantigen in GD, but the antibodies against TSH-R (TSH-R Abs) occur also in some patients with HT. Both diseases present anti-thyroid peroxidase (TPO Abs) and anti-thyroglobulin (Tg Abs) antibodies in different percentages[2]. TSH-R Abs present three subtypes: stimulating (TSAb), blocking (TBAb) and cleavage/neutral immunoglobulins[3,4]. All major thyroid autoantibodies show a transplacental passage, but only TSH-R Abs may induce transient thyroid dysfunction in fetus and newborn[5]. Thyroid functionality is controlled by the balance between TSAb and TBAb. In hypothyroidism, dominate TBAb, in hyperthyroidism dominate TSAb and in euthyroidism both antibodies are equally present or disappeared[6,7]. Clinical observations reveal that GD and HT may follow one another in the same individual. The conversion from GD to HT and vice versa was documented in literature[4,8-11]. It was demonstrated that TSAb, TBAb and TSH-R-binding inhibiting immunoglobulins (TBII) can occur in the same patient. This dual positivity may explain the variable and sometimes unpredictable clinical presentation seen in some AITD cases[4,12]. The balance between TBAb and TSAb can be shifted due to thyroid hormone replacement therapy or antithyroid drugs (ATDs) administration. Both therapies can alter the levels of thyroid antibodies, swinging the balance from hyper-to hypothyroidism or vice versa[13].

The conversion of GD to HT or vice versa in the same individual was described as fluctuating (oscillating, swinging) thyroid functionality. A thyroid disorder with swinging or oscillating thyroid functionality is defined as a clinical and biological entity, characterized by periods of hyperthyroidism and hypothyroidism, having in the background an AITD. The most common phenomenon is the switch from GD into HT, whereas the conversion from HT into GD seems to be less common.

The present paper describes the evolution of fluctuating thyroid function in a group of patients with AITD, detailing the clinical, hormonal and immunological data of the cases.

SUBJECTS AND METHODS

The study was an observational prospective one, performed in the Department of Endocrinology, University of Medicine and Pharmacy, Timisoara, Romania, between 2014 and 2020. It was approved by the local ethics committee and all subjects provided their written consent to be included in the study.

The inclusion criteria for GD were as follows: suppressed TSH (<0.55 mIU/L); elevated levels of free thyroxine (FT4>22 pmol/L) and/or free triiodothyronine (FT3 >6.47 pmol/L), increased serum TBII titers (>1.75 U/L), high levels of TPO Abs, ultrasonographic thyroid pattern consistent with AITD and no tendency to spontaneous normalization before antithyroid drug therapy. The inclusion criteria for the diagnosis of HT were increased TSH levels (>4.78 mIU/L), serum TPO Abs levels above the upper limit of the reference range, ultrasonographic thyroid pattern suggestive for AITD and the absence of serum TBII.

The following data were recorded: age at diagnosis, type of thyroid dysfunction, duration of time until hypo-, respectively hyperthyroidism occurred, TSH, FT3, FT4 at diagnosis and at the time of switch to hypo- or hyperthyroidism, TPO Abs, Tg Abs and TSH-R Abs titers in the hypo- and thyrotoxic phase, occurrence of Graves' ophthalmopathy and type of treatment (levothyroxine or ATDs).

Thyroid morphology (volume, vascularization, internal structure) was assessed by B-mode and color Doppler ultrasonography, using a linear transducer of 7.5MHz.

Third generation TSH was determined by commercial kits (Architect i2000, Abbott Diagnostics), normal values were considered between 0.46 and 4.67 mIU/L. FT4 and FT3 were measured by chemiluminescent magnetic microparticle immunoassay (CMIA, Architect i2000, Abbott Diagnostics), normal ranges were as follows: FT3: 3.54-6.47 pmol/L, FT4: 10-22 pmol/L.

Antithyroid antibodies were measured by CMIA, using Abbot Ax SYM System. The normal values were <60 IU/mL for TPO Abs and <60 IU/mL for Tg Abs. TSH receptor antibodies determined by electrochemiluminescence immunoassay analyzer (ECLIA, Cobas, Roche) represented thyroid-binding inhibitory immunoglobulins, the upper normal limit was set at 1.75 IU/L.

The patients (all females) with fluctuating thyroid functionality were classified as following:

A. Patients with conversion from GD to HT (5 cases)

B. Patients with conversion from HT to GD (3 cases)

C. Cases with recurrent cycling of thyroid functionality, including hyper-and hypothyroidism (2 cases).

RESULTS

Group A: Conversion from GD to HT

Group A included five patients in which thyroid function shifted from hyperthyroidism to hypothyroidism. The patients were followed for a mean duration of 45.6 months. During the thyrotoxic phase, the mean age of the patients was 39.4 years. Thyroid volumes were normal, excepting one case (case 2, patient initials DC), which showed increased values (17.3 mL). Thyroid functionality revealed generally a severe thyrotoxicosis (mean TSH: 0.0038 mIU/L, mean FT4: 34.06 pmol/L, mean FT3: 7.9

Table 1: Conversion from Graves' disease to Hashimoto's thyroiditis (group A)

Parameter (normal values, units)	Thyrotoxic phase					Hypothyroid phase				
	Case 1 (PO)	Case 2 (DC)	Case 3 (GR)	Case 4 (MM)	Case 5 (ME)	Case1 (PO)	Case 2 (DC)	Case 3 (GR)	Case 4 (MM)	Case 5 (ME)
Age (years)	41	31	25	34	66					
Thyroid volume (mL)	9.1	17.2	13.4	15.0	14.8	8.0	17	10.6	15	14.5
TSH (0.55-4.78 mIU/L)	0.001	0.003	0.005	0.008	0.002	131.8	87	23.9	32	19.4
FT4 (10-22 pmol/L)	40	50	24	25.3	31	3.6	5.2	8.6	8.2	8.7
FT3 (3.54-6.47 pmol/L)	8.3	9.0	7.21	7.41	7.62					
TSH-R Abs (<1.75 IU/L)	38	40	9.70	37.50	12.20					
TPO Abs (<60 IU/mL)	870	1200	120	>1300	1000	>1300	573	>1300	1200	
Switch to first episode of hypo- (months)	15	8	24	3	10					

TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; TSH-R Abs: TSH receptor antibodies; TPO Abs: thyroid peroxidase antibodies

pmol/L). TBII presented increased levels, with a mean of 27.4 IU/L. Increased TPO Abs titers were detected in all patients. The functional switch to hypothyroidism was observed after a mean period of 12 months, each thyroid functional status lasting several months. Thyrotoxicosis was treated with ATDs alone (cases 1, 2 and 3) or "block and replace" therapy, associating ATDs and levothyroxine (cases 4 and 5) (Table 1).

In the hypothyroid phase, the thyroid volumes remained unchanged for most of the patients, decreasing insignificantly in one case (patient 3). Thyroid functionality was severely altered (mean TSH: 58.8 mIU/L, mean FT4: 6.86 pmol/L).

The evolution of case 1 (patient initials PO), monitored for 5 years, is characterized by a succession of thyroid function fluctuation (hyper-hypo-hyper-hypo). We believe that in the determination of the first episode of severe thyroid hypofunction, an iatrogenic incident was also implied (high initial doses of methimazole were maintained for one year without monitoring). At present, the patient presents stable thyroid hypofunction under substitution treatment with levothyroxine.

The evolution of patient 3 (patient initials GR), monitored for 8 years, is characterized by a complex succession of thyroid functionalities (hyper-hypo-hyper -finally hypothyroidism). The initial period of thyrotoxicosis lasted 25 months, the first hypothyroid period 36 months, the second thyrotoxic period 2 months, finishing with definitive hypothyroidism. Each phase was treated accordingly (with ATDs, respectively levothyroxine) (Fig.1).

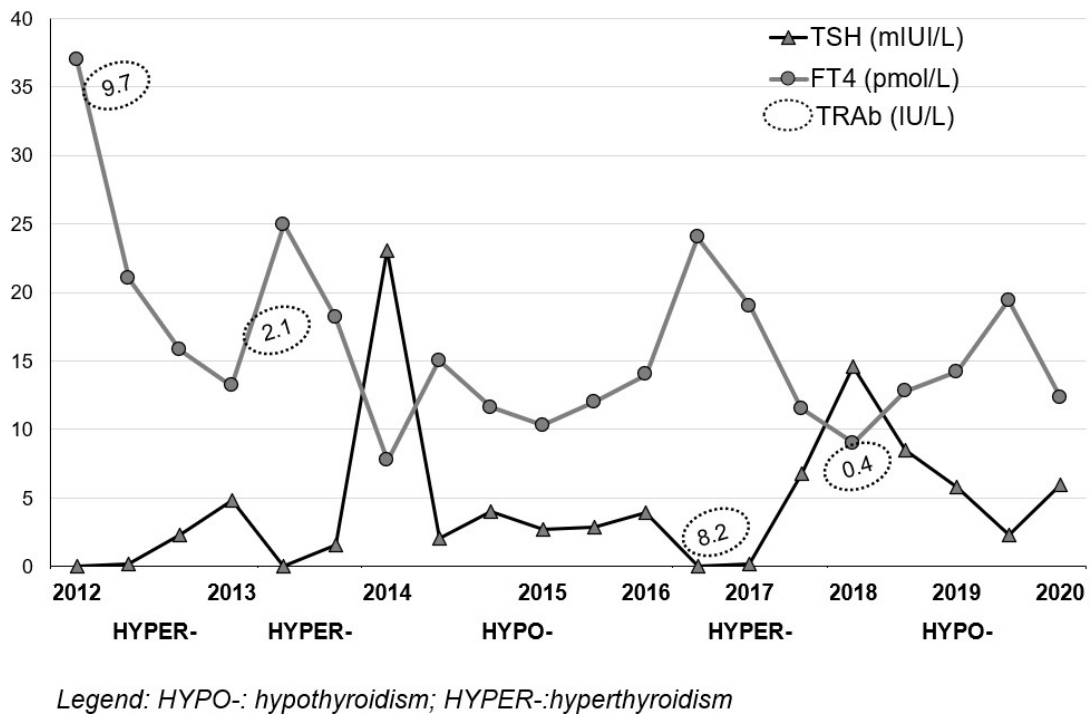

Figure 1: Visual trends in TSH and FT4 levels (group A, case 3, 25 yrs. old)

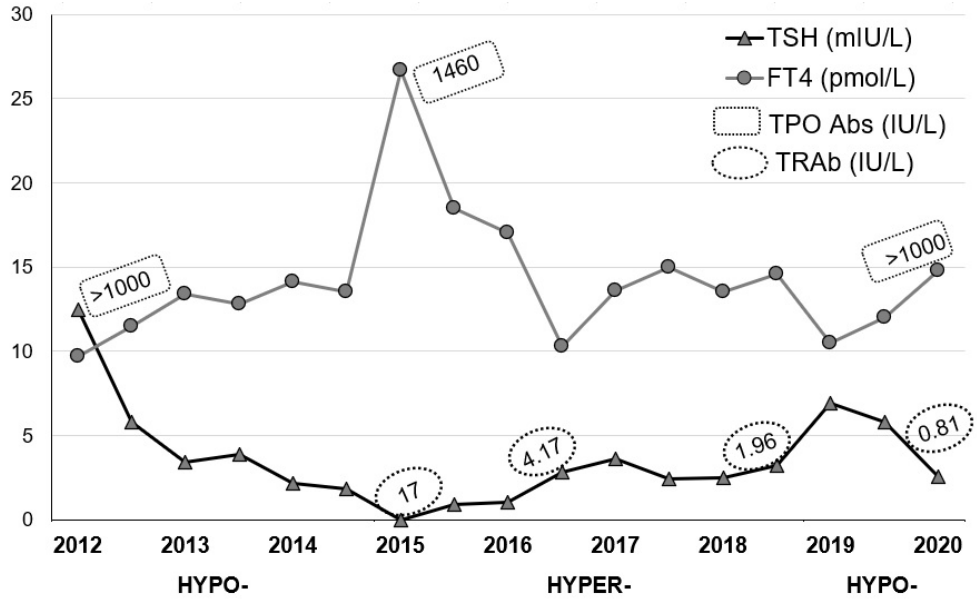

Figure 2: Visual trends in TSH and FT4 levels (group B, case 1, 37 yrs. old)

Group B: Conversion from HT to GD

Group B included three hypothyroid patients who developed thyrotoxicosis after few months or decades of established thyroid insufficiency. Initially, the cases were proven to have Hashimoto's disease, based on clinical, functional and immunologic markers. The case RN presented serum negative autoimmune thyroiditis from the first presentation. All patients became euthyroid on levothyroxine substitution therapy, but afterwards developed clinical and biochemical autoimmune hyperthyroidism, needing ATDs treatment. Thyroid volumes did not change during hypo- or hyperthyroid state. The switch period from hypothyroidism to first thyrotoxic episode varied from 24 months to 20 years. All patients presented in the thyrotoxic phase had significantly increased TBII values (Table 2). In the thyrotoxic phase, two patients also developed infiltrative ophthalmopathy (patients' initials DR, RN).

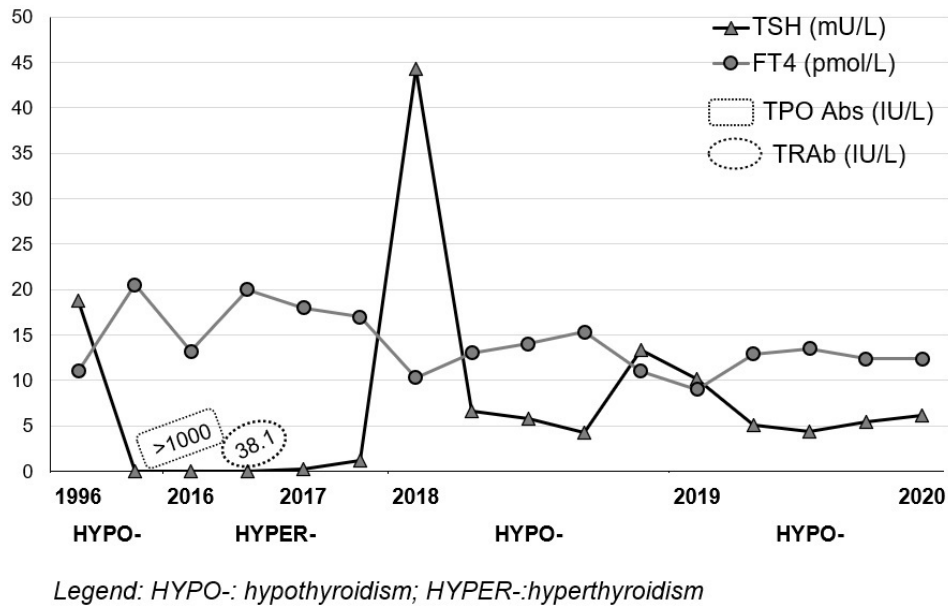

Figure 3: Visual trends in TSH and FT4 levels (group B, case 2, 66 yrs. old)

Table 2: Conversion from Hashimoto's thyroiditis to Graves' disease (group B)

Parameter (normal values, units)	Hypothyroid phase			Thyrotoxic phase		
	Case 1 (DC)	Case 2 (DR)	Case 3 (RN)	Case1 (DC)	Case 2 (DR)	Case 3 (RN)
Age (years)	37	45	42			
Thyroid volume (mL)	10	17.8	11	9.8	17	11
TSH (0.55-4.78 mIU/L)	12.5	18.8	9.5	0.005	0.004	0.05
FT4 (10-22 pmol/L)	9.7	9.5	10.2	26.7	20.5	25.4
FT3 (3.54-6.47 pmol/L)				10.5	7.2	6.9
TSH-R Abs (<1.75 IU/L)				17	38.1	2.24
Anti TPO (<60 IU/mL)	>1000	NA	<60	1460	>1000	<60
Switch to first episode of hyper- (months)	48	240	24			

TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; TSH-R Abs: TSH receptor antibodies; TPO Abs: thyroid peroxidase antibodies

Patient 1 (initials DC), presenting initially documented autoimmune hypothyroidism, was successfully treated with LT4, developed thyrotoxicosis spontaneously, and then returned to hypothyroidism after ATDs therapy (Fig.2).

Patient 2 (initials DR) presented oscillating thyroid functionality, including both hyperthyroidism and hypothyroidism. The patient was initially diagnosed with autoimmune hypothyroidism and treated with levothyroxine for several months (in 2016) (Fig.3). After 20 years, the quiescent status was disrupted by the occurrence of GD associated with mild infiltrative orbitopathy (Fig. 4). After 12 months of ATDs, she developed definitive hypothyroidism (TSH: 44.5 mIU/L), which imposed long-term treatment with L-thyroxine. The thyroid functional succession was as follows: hypothyroidism- euthyroidism and subclinical hypothyroidism episodes - GD - final hypothyroidism.

Patient 3 (initials RN) developed clinical signs of thyrotoxicosis after two years of hypothyroidism, treated with L-thyroxine. She also developed a mild form of orbitopathy, which improved with local measures. She responded promptly to ATDs administration, and after six months of treatment, the values of TSH and FT4 are still maintained in the normal range, TSH-R Abs values being slightly above the upper limit (1.95 IU/L).

Group C: Recurrent cycling of thyroid functionality, including hyperthyroidism and hypothyroidism

Two patients with initial GD (patients' initials IR and BP) presented recurrent cycling of thyroid functionality, including thyrotoxicosis and hypothyroidism.

BP, a girl in early puberty, 12 years old, was initially diagnosed with severe GD. From the beginning, she presented recurrent cycling of thyroid function, including both hyperthyroidism and hypothyroidism, over a 3-year period. Both functionalities were observed with close serial monitoring. Maintenance of stable TSH and FT4 levels was not possible with a regular dose over an extended period. She presented only few short periods of normal thyroid function under therapy. The remitting and relapsing sequence revealed a complex and unsettled clinical course (Fig.5).

Regarding the autoimmune determinations, the patient BP presented in all stages (hypo-, hyper) extremely high titers of TPO Abs (over 1000 IU/L). Thyroid-stimulating immunoglobulin (TSI) determination was not available routinely until 2019, and therefore the patient was evaluated in the first two years by TBII, and afterwards by TSI. TBII values were increased in 2017 at diagnosis (21.8 IU/L) and decreased after 15 months of ATDs to 2.8 IU/L (normal value <1.75 IU/L). TSI increased significantly at the beginning of the last hyperthyroid episode (59.9 IU/L), decreasing after 14 months of ATDs (to 6.47 IU/L,

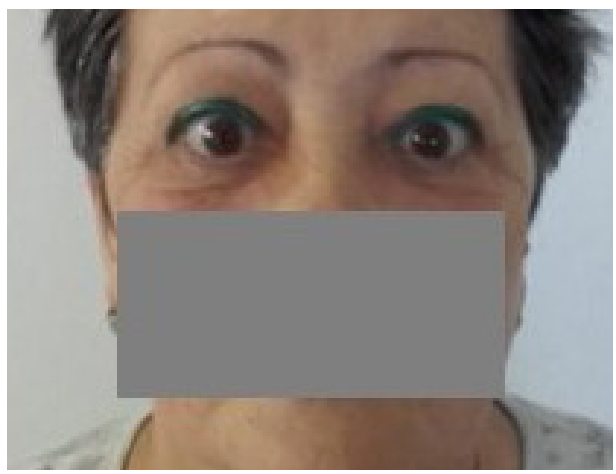

Figure 4: Mild inactive ophthalmopathy developed during thyrotoxic phase in patient DR (group B, case2)

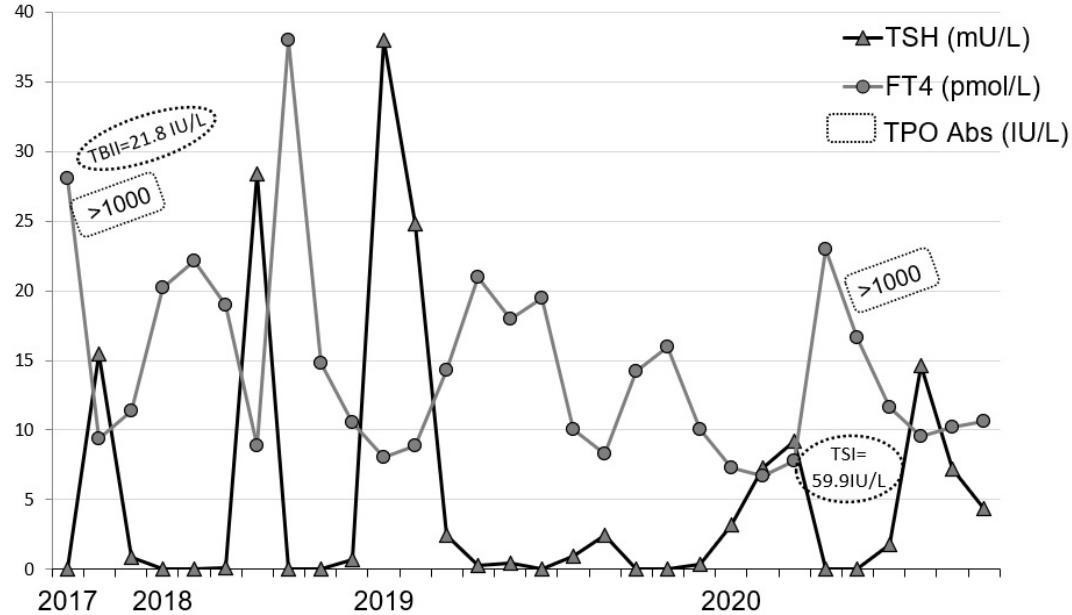

Figure 5: Visual trends in TSH and FT4 levels (group C, patient BP, 12 yrs. old)

normal value <0.10 IU/L). As thyroid hormones and TSH levels have been normal in recent months, total thyroidectomy was recommended.

Patient IR, 68 years old, was diagnosed with GD three years ago. Treatment with ATDs commenced, but after few weeks, she developed clinical hypothyroidism and was treated accordingly. A few months later, under L-thyroxin treatment (with stable, normal TSH values), suppressed TSH and positive TSH-R Abs titers confirmed thyrotoxicosis. She continued to present several hyper-hypo phases, until she recently consented to surgery.

DISCUSSION

Swinging thyroid function has been recently recognized as a distinct entity of AITD. The number of reported cases is generally low and the therapeutic approach is not standardized.

The switching of hyperthyroidism to hypothyroidism is considered uncommon in GD, being more frequently encountered as the switching of hypothyroidism to hyperthyroidism[13,14]. A possible reason for this may be an early referral of the cases for definitive treatment (total thyroidectomy, radioiodine), eliminating thus the possibility for spontaneous oscillations of thyroid functionality. This type of switching was first reported by Hedley in 15-20% of cases diagnosed with GD[15]. Previously, it was thought that cases with GD have only stimulating TSH-R Abs, but now it is recognized that both TSAb and TBAb can be concurrently produced in the same GD patient. The prevalence of TSH-R Abs varieties in different AITD entities is controversial[3,16].

More recently, it was stipulated that the spontaneous transition from hyperthyroidism to hypothyroidism may be explained by two mechanisms.

An unexpected occurrence of TBAb, which induces hypothyroidism after ATDs administration, was reported in approximately 23% of cases with GD, who developed thyroid insufficiency associated with TBAb and a decrease of goiter size[14,17].

The conversion of stimulating to blocking antibodies is favored by ATDs. The treatment with ATDs reduces thyroid autoimmunity, respectively TSH-R Abs and TPO Abs titers, by acting on lymphocyte subsets and thyroid autoantibody synthesis. In cases with both TSH-R Abs types, after ATDs, the balance could switch from TSAb to predominantly TBAb, inducing hypothyroidism[13,14,18].

Another mechanism behind thyroid functional oscillations is the process of thyroid damage, reflected in chronic lymphocytic thyroiditis, which may overcome the stimulatory effects of TSAb and eventually of TSH. The concentrations and affinities of TSAb and TBAb for TSH-R play a critical role in the switch process[13].

The management of this condition is challenging. Three therapeutic options could be considered during the thyrotoxic phase: pharmacological treatment (single or double therapy), thyroidectomy or radioiodine ablation. Methimazole reduces the proliferative activity of CD3+ T cells in pediatric GD patients and increases the proliferation rate of regulatory T cells[19]. Significant changes of lymphocyte subsets, as the reduction of thyroid antibodies, support a direct or mediated effect of the drug on the immune system[20].

The optimal timing for ablative therapy is still unclear, as the duration of thyrotoxicosis phases are variable. For instance, in patient 3 in group A (initials GR), the thyrotoxic phase lasted only two months, followed by definitive hypothyroidism. In group 3, surgery was recommended in both patients as a definitive treatment of the recurrent cycling of thyroid function. These repetitive episodes of hyperthyroidism and hypothyroidism are difficult to manage and monitor in the long-term and ablative therapy seems most appropriate in these patients.

If the patients refuse or present contraindications for the ablative therapy, the best option is to monitor closely and treat each phase with ATDs or L-thyroxine, or treat with block-and-replace regimen.

The conversion from HT to GD (plastically depicted as "from famine to a feast") seems to be less common. This type of switch is also known as "hypothyroid Graves' disease", being first described by Wyse in 1968[21]. The prevalence of this clinical situation is estimated from 1.2% to 5.9% of studied cases[9,14]. In both instances, the initial number of monitored cases was low (24 vs. 34). This conversion was described as prevalent (25.7%) in children with Downs or Turner syndrome[22]. The pathophysiology underlying the conversion of HT to GD remains largely unknown. Levothyroxine treatment may increase TSAb based on a mechanism involving dendritic cell and T-regulatory cell[11,13,23,24]. Some authors reported a positive correlation between levothyroxine doses and TSAb (an increase in levels or occurrence of *de novo* TSAb) [13,14]. This fact can be fortuitous or can be explained by a regulatory effect of levothyroxine on the immune response. Another proposed mechanism refers to the recovery from thyroid damage, initially severe enough to cause hypofunction. After thyroid tissue recovery, it may be stimulated by TSAb[25,26]. Recovery of hypothyroidism has been reported in goitrous forms parallel with TBAb disappearance and TSAb occurrence[14].

The differential diagnosis of this type of swinging comprises many conditions, the most frequent being: levothyroxine overdose, Hashitoxicosis and assay artifact from biotin use. When a patient with HT presents symptoms and signs of thyrotoxicosis, the most likely cause is over-replacement with levothyroxine. In hashitoxicosis, thyrotoxicosis phase is transient, lasting 1-5 months and usually the patients have no TSH-R Abs in serum. Many immunoassays use biotin-streptavidin interaction as an immobilizing system. Biotin, being a small molecule can readily be incorporated into a hormone or an antibody to that hormone. Pharmacologic biotin levels may induce interference in immunoassays (containing biotin-streptavidin) of hormones, which mimic the laboratory changes from thyrotoxicosis[27].

Rapid oscillations in thyroid functionality were rarely described in adults and exceptionally in the pediatric age. This functional aspect can be explained by the simultaneous presence of TSAb and TBAb in the sera of patients[14,28].

The conversion from HT to GD has been reported also in pregnancy[29,30]. Different pregnancy-related changes (immune suppression and/or hemodilution) are probably responsible for the shift in the antibody's properties. The balance between stimulating and blocking TSH-R Abs may impact the clinical presentation of both mother and fetus. Oscillating thyroid functionality was described after therapy with interferon, alemtuzumab and checkpoint inhibitors. Alemtuzumab is a monoclonal antibody used in treatment of multiple sclerosis, that binds CD52, a membrane glycoprotein on T and B lymphocytes and monocytes, leading to lysis and depletion of these cells. The drug may induce thyroid dysfunction (in less than half of cases), represented by GD with a fluctuating course (the most common), but also hyperthyroidism with negative TSH-R Abs, hypothyroidism (TSH-R Abs positive or negative) and HT. The thyroid dysfunction develops months to years after treatment, imposing surveillance for at least four years[31,32].

The medical treatment of oscillating thyroid functionality is performed mainly with block and replace regimen, which improves stability over short to intermediate term. This therapy imposes long-term close monitoring. Radioactive iodine can be performed only in the thyrotoxic phase, but it can aggravate orbitopathy. It can be considered also in children over 10 years of age. Thyroidectomy is recommended, especially in patients with ophthalmopathy and in patients with frequent switches in thyroid function.

CONCLUSION

AITD with oscillating thyroid functionality represents an underestimated and obscure syndrome for many clinicians. A positive diagnosis may be difficult and implies a longstanding observation of patients with thyroid functionality tests and immune markers monitoring. The unpredictability and complexity of thyroid dysfunctionality should raise the suspicion of this phenomenon as soon as possible.

Behind oscillating thyroid functionality several mechanisms have been postulated. Further research like genome screening is needed to help identify these cases, for elucidation of the mechanisms behind unusual disease course and for potential therapeutic options.

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Original Article

Should Kuwait join global epidemiological research for older people?

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ABSTRACT

Objectives: The study was undertaken to i) review the current status on ageing research in Kuwait and the Middle Eastern countries at large; ii) synthesize results of published literature on aging, frailty and related health issues; and iii) identify gaps, highlight the current need and future agenda for ageing research in Kuwait.
Design: We performed a scoping literature review on Medline (via Ovid) to identify key papers that specifically studied older populations (aged ≥60 years) in the Middle East region including the topics addressed in these studies.
Setting: Middle East Region
Subjects: Older people aged 60 years and above
Intervention: Studies reporting older populations
Main outcome: Synthesis of results on frailty and other age-related conditions published in journals originating from Kuwait and other Middle Eastern countries.
Results: We found that frailty research in the Middle East is not well developed, 41 out of 49 of the studies from the Middle East were cross sectional study design covering common conditions related to older age such as falls, depression, cognitive dysfunction (Alzheimer's Disease and Dementia), disability, physical activity, malnutrition, health related quality of life among elderly, polypharmacy and inappropriate prescribing. Fewer studies were found covering frailty and ageing in Kuwait and other countries in the Arab World.
Conclusion: There is a need for research in older population studies in Kuwait focusing on prevalence, determinants, and outcomes of physical and mental frailty.

KEY WORDS: aged, frailty, Middle East, prevalence, risk factors

INTRODUCTION

In 1974, the World Health Organization's Expert Committee defined an elderly person as an individual aged sixty or sixty-five years old, considering that this age is consistent with retirement age across the world[1,2]. Ageing is a global phenomenon where the proportion of older people has been rapidly increasing due to increased longevity and decreased fertility coupled with epidemiological transition with reduced mortality from infectious diseases at a younger age. The United Nations (UN) Population Division indicates that the proportion of the global population aged 60 years or over increased from 8.5% in 1980 to 12.7% in 2017. It is projected to continue to rise over the coming decades, reaching 16.4% of global population in 2030[3-6].

Ageing involves progressive decline in the functions of multiple organs and systems due to limitation in functional reserve, damage from environmental agents, increased prevalence of chronic diseases and the emergence of a number of conditions termed geriatric syndromes[7,8]. Frailty is one of the geriatric syndromes: it is defined as a state of age-related physiologic vulnerability resulting from impaired homeostatic reserve and a reduced capacity of the organism to withstand stress[9]. Frailty is prevalent

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in older adults and is often under diagnosed as an inevitable consequence of aging.

Although population is aging in both developed and developing countries, the 10 countries with the highest proportion of 60+ population are all in the developed world. Japan had 31% of 60+ population in 2011 and is expecting a rise up to 42% by 2050. For Italy (27%) and Portugal (24%), the rise will be up to 38% and 40% respectively. However, the UN projects that in 2050, there will be 42 countries with higher shares of 60+ population than Japan has now. Interestingly, the rapid increase in ageing is reported primarily from relatively newly industrialized or developing countries. For example, Singapore had 23% of 60+ population in 2011 and is projected to increase by more than 10% (38%) by 2050. Similarly, Cuba is expecting a rise up to 39% by 2050, compared to 22% in 2011, and will potentially enter the list of top ten countries with highest shares of older population[5].

The United Nations Sustainable Development Goals (UN SDGs, also known as the Global goals) has Health as a central focus in SDG 3 (Ensure healthy lives and promote well-being for all at all ages). The World Health Organization promotes healthy ageing as a commitment to SDGs, which is about preserving both physical and mental capacity for elderly people, while making changes to the environments (housing, transportation, public spaces etc.) so that they are accessible to and supportive for older people with varying needs and capacities[6]. In addition to physical ailments, older people face many social problems. Hence, in addition to governmental organisations, there are several charity organisations across the world which focus on medical and social needs of older people. Regarding the identification of the older population as a vulnerable age group and the commitment to improve their health and wellbeing, most of the studies in the older adults are conducted in developed countries[10-13].

Therefore, the purpose of this paper is to provide an overview of research conducted in older population in developing countries, specifically focussing on the Middle East countries. This will highlight the needs that are unmet in these countries.

MATERIALS AND METHODS

Scoping of the literature was conducted systematically to identify key papers from the Middle East exploring areas of research relevant to older population. A search was undertaken on Medline (via Ovid) from 2016 to 5th week of January 2021 using a systematic approach with a search strategy (appendix 1) MeSH terms (frailty, aged, prevalence, risk factors, determinants with "social determinants of health "as subheadings) and relevant key words (frailty, aged, older people prevalence, risk factors, determinants) were used to identify studies that assessed prevalence, risk factors, social determinants and frailty among older people. These terms were initially combined appropriately using the Boolean operators 'OR' and 'AND'. These were then combined with the countries from Middle East to identify the research conducted

Table 1: Number of older population studies by country and topic from the Middle East

Country	Older population studies	Topics	Frailty studies
Bahrain	1	depression	N/A
Egypt	8	malnutrition, falls, osteoporosis screening tools, depression, psychological risk factors for immigrants, assessment of the physical, nutritional, and psychological health status	
Gaza Strip & West Bank	1	disability	N/A
Iraq	1	radiotherapy	N/A
Jordan	3	dementia, Alzheimer's' disease, physical, psychological and social well-being	N/A
Kuwait	1	polypharmacy	N/A
Lebanon	14	nutritional status, delirium, symptom prevalence, malnutrition, depression scale, needs assessment, cognitive function, dementia, inappropriate medications, self-rated health, social isolation, mental disorders, carriage of beta-lactamase-producing Enterobacteriaceae	N/A
Oman	1	inappropriate prescribing	N/A
Qatar	3	polypharmacy, inappropriate prescribing, risk factors for ICU admission	N/A
Saudi Arabia	15	venous thromboembolism, inappropriate medications, in-hospital mortality, assessment of frailty, Alzheimer's' disease, colorectal cancer screening, drug interactions, delirium, risk of falls, malnutrition, epilepsy, prevalence of elongated styloid process, depression, the impact of hyposalivation on Quality of Life and oral health	N/A Yes
Syria	0	N/A	N/A
United Arab Emirates	1	fall related injuries	N/A
Yemen	0	N/A	N/A

NA: not available; ICU: intensive care unit

in the specific countries. The list of Middle Eastern countries was obtained from the 'World Bank' list[14].

The titles and abstracts of all the identified citations were perused to identify the studies that specifically looked at over 60 populations in the Middle East region countries including the outcomes addressed in these studies. Any studies that had a wider age range of population were excluded.

RESULTS

The number of relevant studies identified by systematic search is shown in Table 1 for each country. When compared to existing contemporary older people research globally, while Western countries focus more on frailty and ageing studies, 41 out of 49 of the studies from the Middle East were cross sectional in design, covering common conditions related to older age such as falls, depression, cognitive dysfunction (Alzheimer's Disease and Dementia), disability, physical activity, malnutrition, health related quality of life among elderly, polypharmacy and inappropriate prescribing. The majority of studies came from Saudi Arabia, Lebanon and Egypt. There was one study from Egypt comparing cognitive functions between late-onset (≥60 years) and early-onset (<60 years) depression to highlight the effect of vascular risk factors in the elderly.

We found one study from Saudi Arabia specifically focused on frailty assessment, which validated the Arabic version of the FRAIL scale in community-dwelling older adults[15]. Another study from Saudi Arabia assessed basic geriatrics knowledge among internal medicine trainees in a teaching hospital, which was not classified as a study of older age[16]. One other study assessed the prevalence and risk of polypharmacy among community-dwelling elderly in Kuwait[17].

DISCUSSION

Systematic search from one of the largest bibliography databases revealed that most of the research in older population in Middle East is focused on several topics related to older age. However, research into rapidly emerging geriatric giant, frailty, is not well developed in the Middle East. The causes for lack of research on frailty as core concept could be potentially due to lack of resources to conduct cohort studies, lack of expertise, or lack of awareness among clinicians and public, and service providers.

Given that the number of studies found in Kuwait is low compared to other countries in the Middle East region, there is a clear need for Kuwait to join global academic research into older age, especially physical and mental frailty. We propose to establish a programme of research in older people in Kuwait through research capacity building and upscaling existing research skills. This ultimately will contribute to the knowledge translatable to clinical practice relevant to older people's conditions including frailty research in Kuwait. For this purpose, the lead author of this paper, Dr. Serri: Senior General Practitioner, Geriatric medicine Department at the Ministry of Health in Kuwait, has proposed for a three-year research program, working with a team of researchers at the University of Aberdeen, Scotland, in the United Kingdom.

The research program is funded by the Civil Service Commission in Kuwait and the overarching theme is to examine the physical and mental frailty among older people in Kuwait, focusing on prevalence of frailty and risk factors for acute hospital admissions in the context of frail older population. This will also form an excellent foundation for continuous professional development through a doctoral training programme to become an independent researcher and flourish Kuwait-UK partnership in health system development in the future.

CONCLUSION

Based on scoping literature, frailty research in the Middle East is not well developed. There is a need for research in older population studies in Kuwait, focusing on prevalence, determinants, and outcomes of physical and mental frailty.

Appendix

We searched Medline (Ovid) 2016 to January week 5 2021. Prevalence, risk factors, determinants with "social determinants of health "as subheadings were used as Mesh terms. Prevalence, risk factors, determinants were used as text words, Mesh terms and text words were combined with (OR). Frailty, aged, were used as Mesh terms. Frailty, aged, older people were used as text words, both Mesh terms and text words were combined with (OR). Then, each country of the Middle East was searched both as Mesh term and text word and combined with (OR). The tree search results were combined with (AND), to explore any studies form the Middle East countries including older population.

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Authors' contribution: Loulwah Serri: literature review and drafting the paper; Amudha Poobalan,

Roy Soiza, Phyo Kyaw Myint: supervision and critical revision. All authors participated in the inception and design.

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Case Report

Phenytoin-induced anticonvulsant hypersensitivity syndrome in a patient with suspected Epstein-Barr virus reactivation associated encephalitis

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ABSTRACT

Anticonvulsant hypersensitivity syndrome (AHS) can be triggered by a reactivation of the Epstein-Barr virus (EBV). We describe a case of a 23-year-old woman with severe phenytoin-induced AHS after suspected EBV reactivation associated encephalitis for the treatment of status epilepticus. An EBV-specific serologic test made the diagnosis of EBV reactivation. Four weeks after taking phenytoin, the patient developed fever and generalized whole body erythematous rash. We suggest that reactivation of the EBV may have contributed to the development of AHS in this patient. In EBV reactivation associated encephalitis, careful use of anticonvulsants is necessary and the possibility of AHS during treatment period must be considered.

KEY WORDS: anticonvulsant hypersensitivity syndrome, Epstein–Barr virus, phenytoin, reactivation

INTRODUCTION

Anticonvulsant hypersensitivity syndrome (AHS) is a potentially life-threatening drug-induced reaction characterized by multi-organ system involvement[1]. Unlike other drug-induced reactions, this syndrome is caused by a limited number of drugs such as phenytoin, carbamazepine, phenobarbital and lamotrigene, and occurs after prolonged exposure to the offending drugs[2]. It has been postulated that viral reactivation may play a role in the development of this syndrome[1,2]. Some case reports have associated AHS with viral reactivation[1-4]; however, AHS associated with viral encephalitis has not been reported. Recently, we experienced a case of the suspected Epstein-Barr virus (EBV) reactivation associated encephalitis causing AHS.

CASE REPORT

A 23-year-old woman visited our hospital due to status epilepticus for 30 minutes. She had developed a headache, fever and chills for 10 days. An electroencephalogram showed continuous irregular theta and delta slowing with spiky activities in the right hemisphere (Fig. 1). After 1000 mg of phenytoin was given intravenously, the convulsive movements disappeared. She was instructed to take 300 mg of phenytoin daily.

Laboratory examinations showed leukocytes at 14,800/μL (neutrophils, 87%), hemoglobin at 15.2 g/dL, platelets at 281,000/μL, erythrocyte sedimentation ratio of 78 mm/hr, C-reactive protein of 11.85 mg/dL, blood urea nitrogen of 20.0 mg/dL, creatinine of 0.9 mg/dL, glucose of 141 mg/dL, fibrinogen of 463 mg/dL, D-dimer of 1430 ng/mL, creatinine kinase of 765 mg/dL, alanine aminotransferase (ALT) of 145 IU/L, and aspartate aminotransferase (AST) of 105 IU/L. Brain imaging performed immediately after seizure control was unremarkable. A cerebrospinal fluid (CSF) analysis was performed, which showed clear colorless spinal fluid with increased opening pressure

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Table 1: The results of the patient's Epstein-Barr virus specific serologic antibody titers.

EBV specific antibody	Initial	Follow-up	Reference (U/mL)
EBV-EA IgM	Borderline (9)	Borderline (7)	Negative <6
EBV-EA IgG		Borderline (7)	Borderline 6~10
EBV-NA IgM	Positive (27)	Borderline (10)	Positive 10>
EBV-VCA IgM	Negative (5)	Negative (4)	
EBV-VCA IgG		Positive (28)	

The initial and follow-up studies were performed one week and four weeks after the seizure developed respectively.
EBV: Epstein-Barr virus; VCA: virus capsid antigen; NA: nuclear antigen

of 260 mm CSF, glucose level of 85 mg/dL, protein of 73 mg/dL, red blood cell count of 2/mm^3, and white blood cell count of 16/mm^3 with 99% lymphocytes. Her EBV real time polymerase chain reaction (PCR) in CSF was negative. Her serum was positive for EBV nuclear antigen (EBV-NA) IgM (titer, 27 U/mL) and borderline EBV-early antigen (EBV-EA) IgM (titer, 9 U/mL) one week after seizure onset (Table 1). For the treatment of viral encephalitis, the patient was treated with acyclovir 1350mg/day (30mg/kg/day) for 14 days. Liver enzymes progressively returned to normal. She was fully recovered without any neurological sequelae.

After four weeks of phenytoin therapy, she developed fever, facial edema and a generalized pruritic erythematous maculopapular rash that spread over the whole body (Fig. 2). Laboratory studies showed mild leucocytosis (12,300/ul) with lymphocytosis (40.3%; atypical lymphocytes, 1%) and eosinophilia (9.3%). Liver function tests were abnormal with increased ALT (255 IU/L) and AST (305 IU/L). Her serum was positive for EBV-virus capsid antigen IgG (titer, 28 U/mL) and borderline for EBV-NA IgM (titer, 10 U/mL) 27 U/mL), EBV-EA IgM (titer, 7 U/mL) and EBV-EA IgG (titer, 7 U/mL) on week 4 after seizure onset (Table 1). Other virological investigations including cytomegalovirus, echovirus, coxsackie virus, herpes virus, varicella zoster virus and hepatitis A virus were all negative. The phenytoin was stopped, and a corticosteroid treatment was started. Ten days after AHS onset, the skin lesions and facial edema began to subside gradually. Corticosteroid was gradually tapered for two weeks, and she was fully recovered from the skin lesions without seizure.

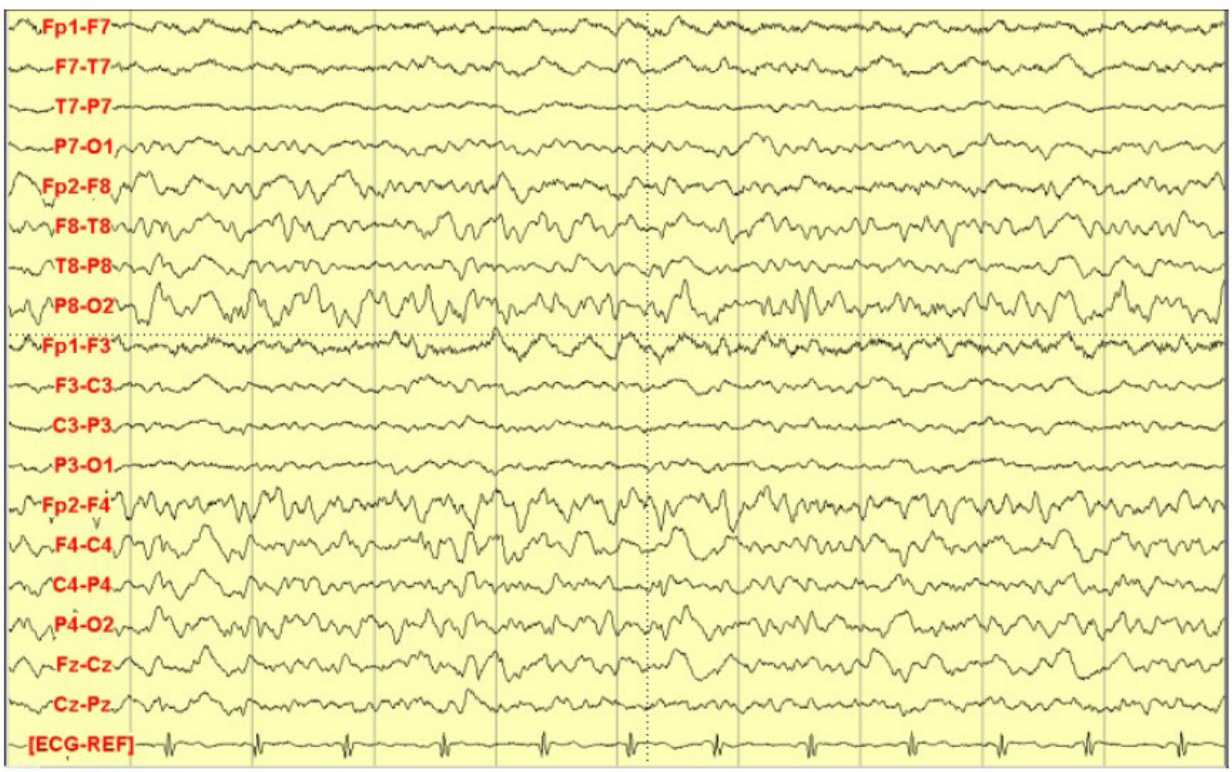

Figure 1: Electroencephalography shows continuous irregular theta and delta slowing with spiky activities in the right hemisphere after phenytoin loading of 1000 mg.

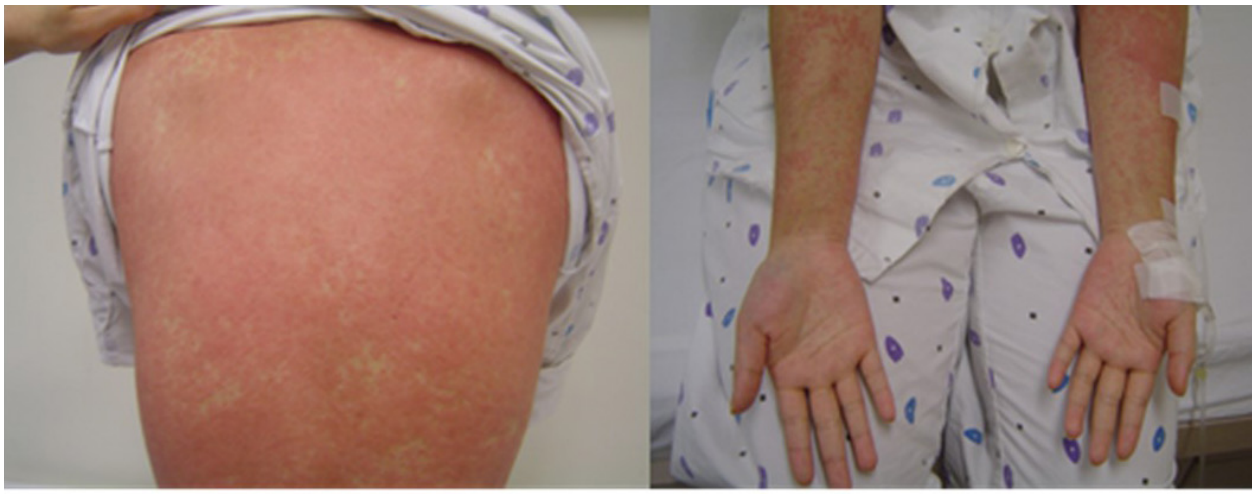

Figure 2: The patient developed generalized pruritic erythematous maculopapular eruptions after 4 weeks of taking phenytoin.

DISCUSSION

The mechanism of AHS by viral reactivation is not clearly understood[3,4]. A viral infection may modify drug metabolism and may induce the production of reactive metabolites[3,4]. The viral receptors for EBV are present on B cells, which are the main site of viral replication[1]. T cells would be activated in response to reactive drug metabolites, and a stimulation of drug specific T cells could induce the reactivation of latent viruses secondarily[2]. Recently, human herpes viruses and human immunodeficiency virus were proposed as possible candidates, because they induce a latent infection, persist in lymphocytes and may reactivate under various conditions[1-4]. In this case, we propose that phenytoin metabolites may have amplified the T cells, and this T-cell activation may have affected the persistence of the EBV infection.

Though the patient showed negative result of the CSF PCR for EBV, the diagnosis of EBV reactivation associated encephalitis was based upon the clinical symptoms, CSF profiles and EBV-specific antibody responses[5]. Though the EBV-NA IgG titer was not detected in this patient, recurrent EBV infection could be demonstrated in consecutive serum titer changes of EBV-EA IgM antibody titer[6]. The nervous system involvement of EBV may be the result of infected cells infiltrating the neural tissue directly or inducing a secondary inflammatory reaction that causes indirect neuronal involvement[5,6]. Considering her favorable clinical course and mild CSF leukocytosis, the encephalitis of the patient probably resulted from a direct infiltration of the reactivated EBV rather than an EBV-associated immune response. However, we could not confirm EBV DNA in PCR in this patient.

Some of the patients with EBV involvement in central nervous system can develop Chronic Active EBV (CAEBV) disease during the clinical course. CAEBV can show various central nervous system complications such as posterior reversible encephalopathy syndrome, basal ganglia calcification and falx cerebri hemorrhage, *etc*. However, most patients showed no neurological symptoms. Long-term follow-up is important to observe the occurrence of CAEBV with neurological complications in this patient in the future[7].

We initially prescribed 300 mg phenytoin daily, because her presenting symptom was status epilepticus. However, we did not apply other antiepileptic drugs after AHS developed because of previous case reports about other antiepileptic drugs such as carbamazepine, phenobarbital and lamotrigine, and their relation to AHS[7].

Considering that EBV associated encephalitis shows a self-limited favorable outcome in most immunocompetent individuals[8], and that AHS is a serious adverse event often resulting in hospitalization[9,10], the use of long-term anticonvulsants must be balanced between the possible benefits and risks in some patients with viral encephalitis.

CONCLUSION

We describe a patient with phenytoin-induced hypersensitivity syndrome of suspected EBV reactivation associated encephalitis. This is the first case report of phenytoin-induced AHS in a patient with EBV reactivation associated encephalitis.

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Case Report

Asymptomatic isolated aortic arch dissection: A peculiar case

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ABSTRACT

We hereby represent a case of a chronic aortic arch dissection in a 69-year-old male who was diagnosed incidentally during cranial computed tomography (CT) angiography scan screening due to transient ischemic attack. Due to asymptomatic nature, size and a follow up period of one and six months with no noticeable changes, we recommended medical follow up of every six months with thorax CT angiography scan.

KEY WORDS: aorta, cerebrovascular accident, dissection

INTRODUCTION

In cardiovascular surgery, aortic dissection is one of the emergency and dramatic pathologies associated with high morbidity and mortality[1,2].

Aortic dissection is generally suspected based on a patient's history and physical examination. Patients with an aortic dissection presents with severe, sharp or 'tearing' back pain. Asymptomatic aortic dissection has been reported but it is relatively rare[3]. Patients with painless dissection generally have a history of diabetes mellitus and mostly presents with symptoms like syncope, stroke or heart failure[3]. Asymptomatic aortic dissection has been associated with high mortality compared with symptomatic aortic dissection. To the best of our knowledge, no case has been reported with asymptomatic isolated aortic arch dissection.

CASE REPORT

A 69-year-old male patient was presented to a neurologist with transient ischemic attack (TIA). A cranial computed tomography (CT) angiography was taken for diagnosis. He was incidentally identified to have a dissection within the arcus aorta on cranial CT one week after presentation (Figure 1). He was referred to cardiology department for further diagnosis and treatment of a dissecting arcus aorta. His past medical history included hypertension. Also, he had a history of coronary angiography ten years ago and ablation for arrhythmia three years ago. Cardiac examination was performed. Routine investigations were within normal limits. His physical exam showed a heart rate of 86 bpm, blood pressure of 140/80 mmHg, respiratory rate of 13/minute, and oxygen saturation of 98% with no pathological sign in examining. An electrocardiogram showed a normal sinus rhythm. Cardiac echocardiography was performed. Echocardiography revealed normal left ventricle function with mild hypertrophy, and ascending aorta was 39 mm with no sign of dissection.

Due to asymptomatic isolated aortic arch dissection with mild dilatation of ascending aorta of 39 mm, a heart team council recommended medical follow up for a period of one month. Cranial branches and upper extremity branches of aorta were not involved. During follow up period of one month, a thorax CT angiography scan was taken and no changes were observed within an isolated dissecting arcus aorta (Figure 2, 3). Lastly, there was no change in dissecting

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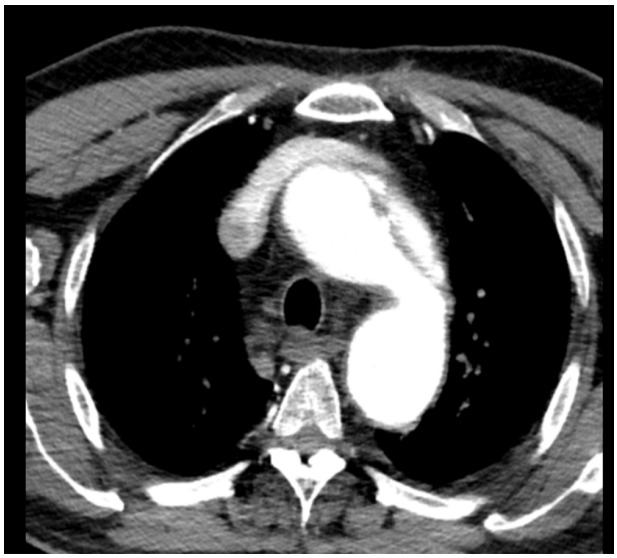

Figure 1: Cranial CT angiography scan showing a dissection of arcus aorta.

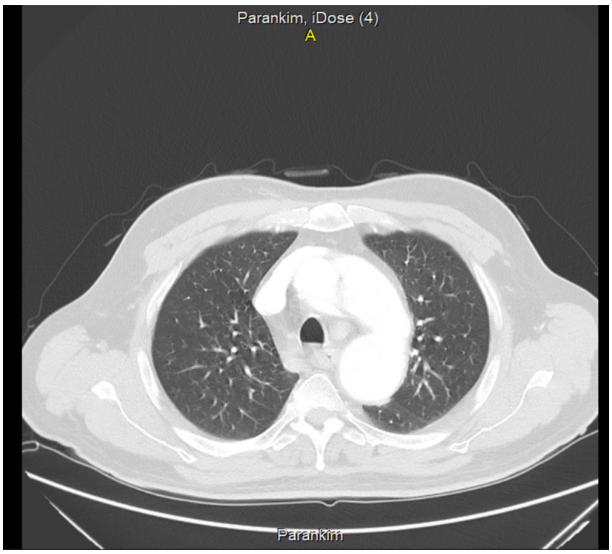

Figure 2: Thorax CT scan showing dissection of arcus aorta during follow up period.

arcus aorta at six month's thorax CT angiography (Figure 4).

DISCUSSION

Aortic dissection occurs when a tear in the inner wall of the aorta causes blood to flow between the layers of aortic wall causing their separation[1]. This condition is more frequent in patients with hypertension, which causes shear stress in aortic wall. Our patient was diagnosed with isolated arcus aortic dissection that seemed to be chronic and may have been associated with hypertension or iatrogenic injury during conventional angiography.

Patients with aortic dissection presents with severe chest pain, acute hemodynamic instability, absence or unilateral peripheral pulses, neurologic complications and aortic insufficiency[4]. Otherwise, syncope, stroke and heart failure were more common signs in painless aortic dissection. It has been shown in a study that nearly 30% of patients with aortic dissection were initially presented with neurologic symptoms[5]. These symptoms were ordered such as ischemic stroke (16%), ischemic neuropathy (11%), syncope (6%), somnolence (4%), and seizures (3%)[6]. Although our patient presented with cerebral vascular event, we believe that TIA was a condition not associated with dissection of arcus aorta and it is for this reason that we regarded dissection of arcus aorta to be asymptomatic. Medical follow-up was recommended in this case.

Thorax CT angiography scan is a diagnostic tool for aortic arch dissection with high sensitivity and

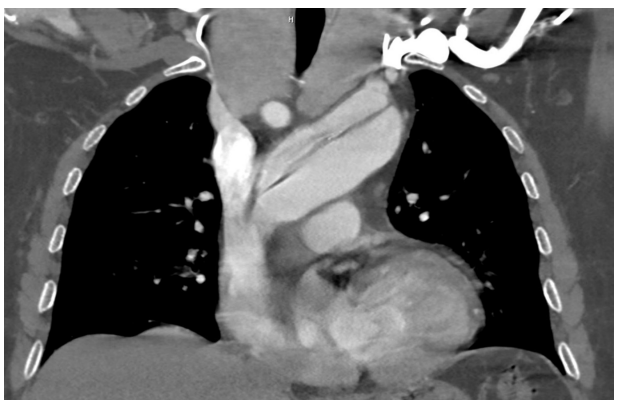

Figure 3: Thorax CT scan showing dissection of arcus aorta at six months follow up period.

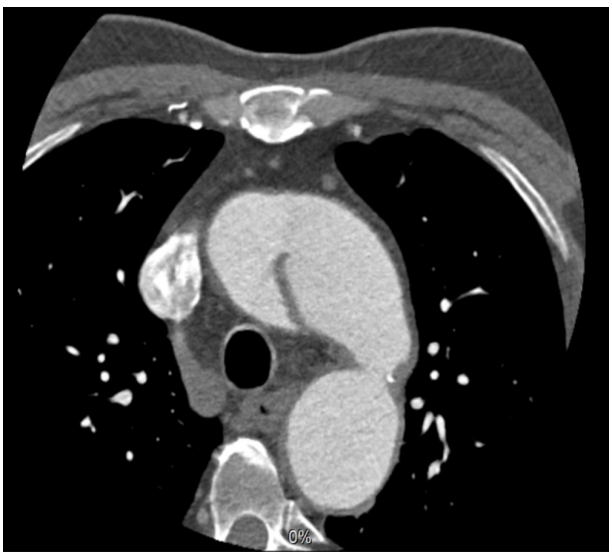

Figure 4: Thorax CT scan showing dissection of arcus aorta at one month in sagittal plane.

specificity. Our patient pathology was incidentally diagnosed with cranial CT angiography scan. Isolated aortic arch dissection is a very rare case and there is no consensus on its treatment[7]. Aortic arch dissection may also be involved in aortic dissection type I and II[8]. The treatment of aortic arch in aortic dissection includes on pump open surgical repair under total circulatory arrest with antegrade cerebral perfusion. Aortic arch repair may also be treated with aortic arch debranching hybrid with endovascular repair or branched stent grafts[8]. Asymptomatic aortic arch dissection are referred for repair depending upon diameter, location, expansion rate, family history of rupture/dissection, and the presence of associated coronary heart disease or valve pathology requiring surgical intervention, with special considerations depending on the presence of underlying contributing etiologies (eg, connective tissue disorders, bicuspid aortic valve, familial thoracic aortic aneurysm/dissection). For patients who meet criteria for repair, survival is improved for open surgery compared with medical therapy alone[9]. Our patient was under medication during the follow-up period and no changes have been reported to occur in our patient.

CONCLUSIONS

Isolated aortic arch dissection is a very rare case and to the best of our knowledge, no cases have been reported. Even when there data on medication is lacking, we decided to medically follow-up with periodic CT scans.

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Case Report

Endovascular treatment of falcine sinus dural arteriovenous fistula: A report of two cases

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ABSTRACT

A dural arteriovenous fistula (DAVF) in the falcine sinus is rare, as is our experience with endovascular treatment (EVT) in such cases. Here, we present two cases of DAVF in the falcine sinus. In case 1, the patient was a 38-year-old male, and in case 2, the patient was a 35-year-old female; both had sudden onset of cerebral hemorrhage. They underwent computed tomography angiography and/or digital subtraction angiography, which showed a DAVF in the falcine sinus. In case 1, the feeding artery was only the right middle meningeal artery (MMA), which drained to the superior sagittal sinus through the cortical vein. In contrast, in case 2, there were a variety of feeding arteries, including bilateral ophthalmic arteries, the internal maxillary artery and the right MMA, and the DAVF drained through both cortical veins and cerebral deep veins simultaneously. Both were cases of Cognard type IV DAVF. Using Onyx (Medtronic, Irvine, California, USA), both patients underwent complete EVT through the MMA, with a satisfactory therapeutic outcome. It is highly feasible to use Onyx to perform EVT for a DAVF in the falcine sinus using an arterial approach through the MMA. However, due to the limited number of cases, we still need to accumulate additional experience.

KEY WORDS: dural arteriovenous fistula, endovascular treatment, falcine sinus

INTRODUCTION

Dural arteriovenous fistula (DAVF) often occurs in the cavernous sinus, transverse sinus, sigmoid sinus, tentorium, etc[1]. The falcine sinus is located in the anterior cerebral falx and is extremely rare in adults[2]. Therefore, DAVF in the falcine sinus is also rare and has been reported in only a few cases[3-5]. DAVF treatment has progressed from microsurgery to endovascular treatment (EVT). At present, the treatment for DAVF in the falcine sinus is mainly EVT[4]. Since DAVF in the falcine sinus is rare, we present two such cases treated with EVT to accumulate experience.

CASE REPORTS

Case 1

The patient was a previously healthy 38-year-old male who was hospitalized for coma an hour after the sudden onset of a headache. A physical examination showed light coma. The muscle strength of the right limb was grade 3, with a positive pathological reflex. Brain computed tomography showed frontal lobe hemorrhage entering the ventricular system (Figure 1A), computed tomography angiography showed a malformed blood vessel in front of the cerebral falx (Figure 1B), and digital subtraction angiography showed a DAVF in the falcine sinus, supplied by a single branch of the right middle meningeal artery (MMA) and draining to the superior sagittal sinus through the cortical vein on the medial side of the frontal lobe. The draining vein was dilated, and Cognard type IV DAVF was diagnosed (Figure 1C-F).

In terms of treatment, a Marathon microcatheter (Medtronic, Irvine, California, USA) was placed at the intersection of the MMA and the anterior falx artery (AFA) using a transarterial approach through the MMA (Figure 2A), and Onyx (Medtronic, Irvine, California, USA) was injected to penetrate the DAVF and beginning of the draining vein (Figure 2B). Subsequently, angiography of the right internal carotid artery and external carotid artery showed complete

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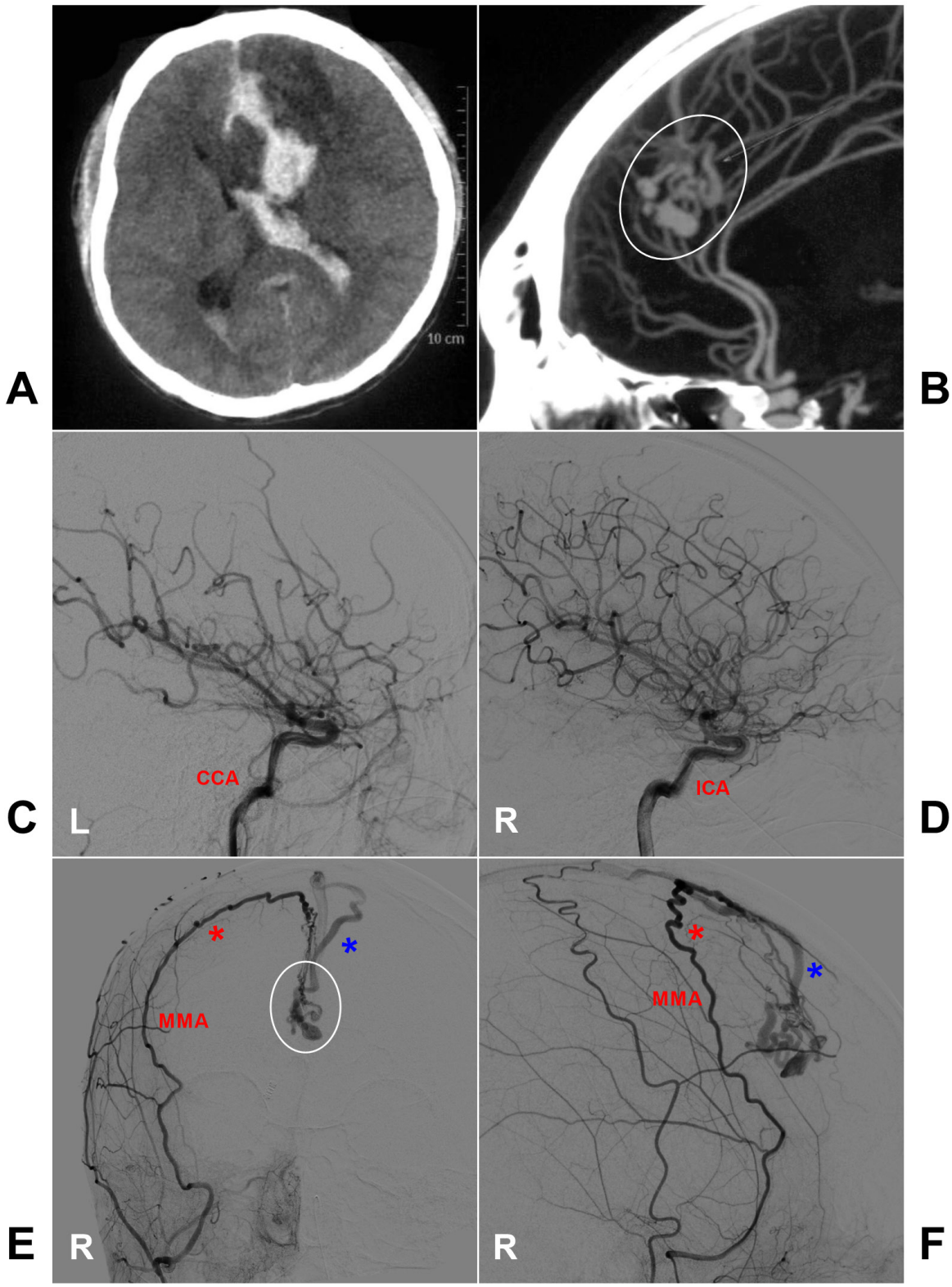

Figure 1: Preoperative images from case 1
A: Brain CT scans showing that the hemorrhage in the longitudinal fissure extended backward into the left ventricular system. **B:** Brain CTA MIP showing that the DAVF was located in the anterior part of the cerebral falx at the midline (ellipse). **C-D:** Arterial-phase angiography showing no abnormalities in the left CCA (C) or right ICA (D). **E-F:** ECA angiography of the right anterior position (E) and lateral position (F) showing that the right MMA (red asterisk) supplied blood to the DAVF (ellipse in Figure E) in the falcine sinus through the posterior part of the AFA and drained to the sagittal sinus through the cortical vein on the medial side of the frontal lobe (blue asterisk), accompanied by tortuous and dilated draining veins. This was a Cognard type IV DAVF.

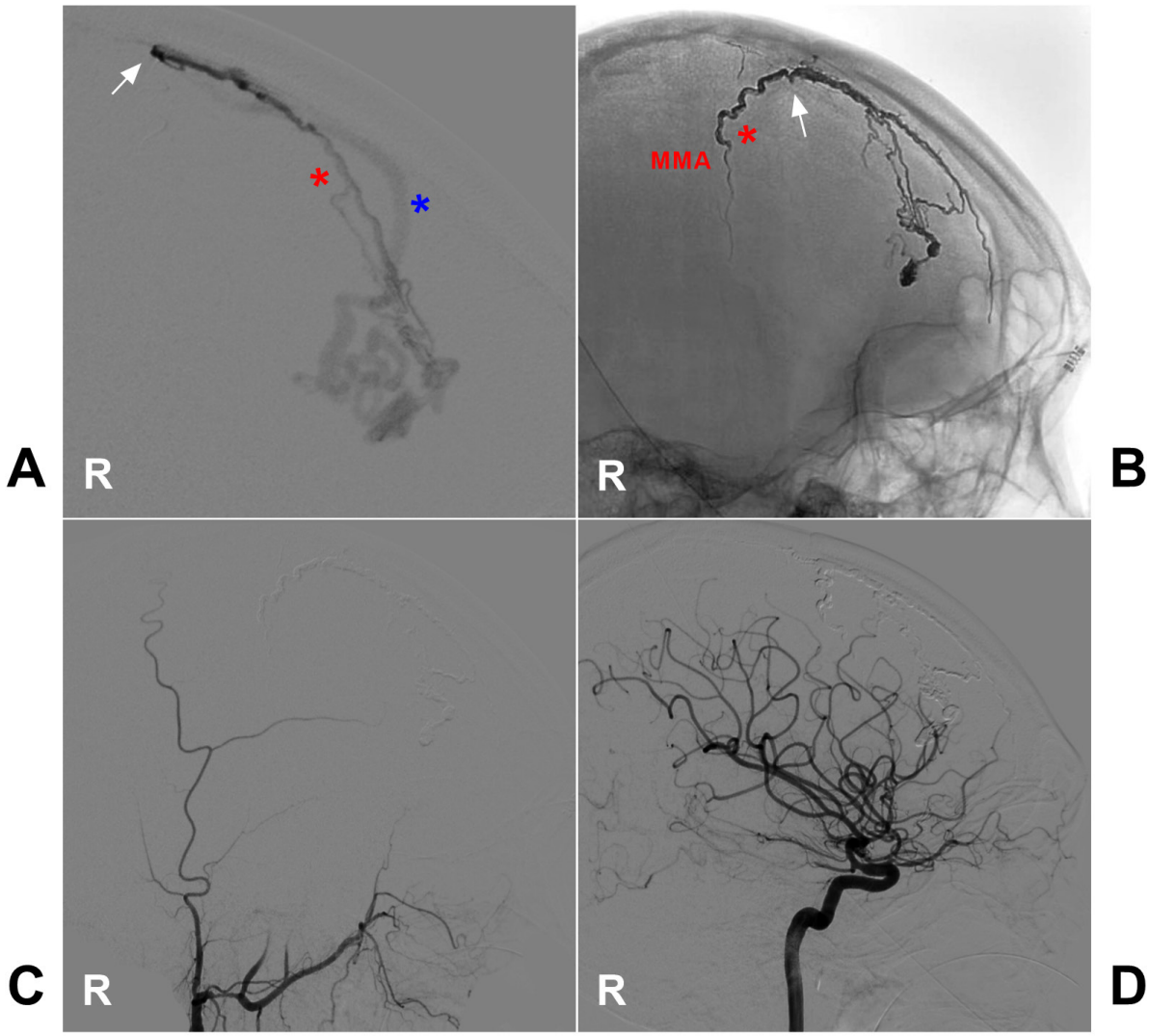

Figure 2: The EVT process in case 1
A: Microcatheter angiography of the right MMA showing that the DAVF was fed by the AFA (red asterisk) and drained through the cortical vein (blue asterisk). The arrow denotes the position of the microcatheter. **B:** X-ray film showing Onyx casting in the DAVF via the MMA and regurgitation of Onyx in the MMA (red asterisk); the arrow denotes the position of the microcatheter. **C-D:** The right ECA (C) and right ICA (D) showing complete DAVF embolization.

embolization of the DAVF (Figure 2C-D). After the operation, the patient received conservative treatment for one week and was then discharged. At the half-year follow-up, the patient was awake and could answer questions correctly, but the right limb remained paralyzed and the patient had lost the ability to live independently.

CASE 2

The patient was a previously healthy 35-year-old female who was hospitalized two hours after the onset of a sudden headache. A physical examination showed that she was lucid and had flexible limbs, neck stiffness and a positive Kernig's sign. Brain computed tomography showed intraventricular hemorrhage (Figure 3A). Digital subtraction angiography showed a DAVF in the falcine sinus, which was fed by the anterior ethmoidal artery from the bilateral ophthalmic artery through the AFA. In addition, the bilateral internal maxillary artery (IMA) was anastomosed with the anterior ethmoidal artery through the vascular network originating from the end branch of the IMA and supplied blood through the AFA and the right MMA. The cortical veins and deep veins on the medial side of the frontal lobe were involved in drainage of the DAVF, and the draining veins were dilated, Cognard type IV DAVF was diagnosed (Figure 3B-F).

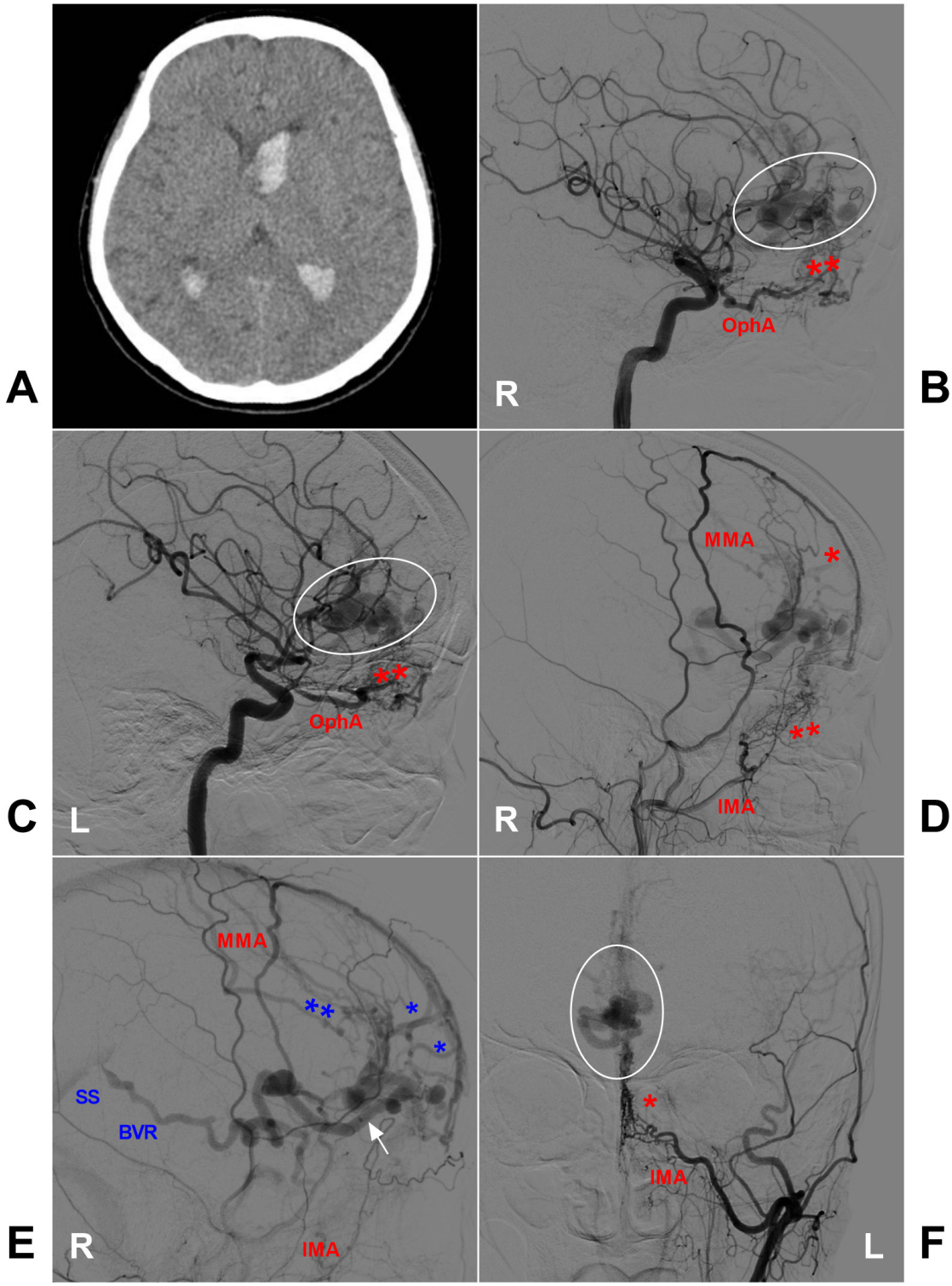

Figure 3: Preoperative images from case 2

A: Brain CT scans showing hemorrhage in the left ventricular system. **B-C:** Arterial-phase angiography of the right (C) and left ICA (D) showing a DAVF in the falcine sinus, which was fed by the anterior ethmoidal artery from the OphA through the AFA (asterisk). **D:** Arterial-phase angiography of the right ECA showing the right MMA passing through the posterior part of the AFA (one red asterisk) and the IMA supplying blood through the arterial network (two asterisks). **E:** Late-phase arterial angiography of the right ECA showing drainage of the DAVF. The blue asterisk indicates drainage of the cortical vein on the medial side of the longitudinal fissure, and the arrow indicates where the DAVF drains through the veins at the base of the frontal lobe and connects backward to the basal vein of Rosenthal (BVR) and SS. The draining veins showed many dilatations; Cognard type IV DAVF was diagnosed. **F**: Left ECA angiography showing that the IMA also supplied blood to the DAVF (asterisk); the ellipse denotes the location of the DAVF in the falcine sinus.

In terms of treatment, a Marathon microcatheter was placed at the intersection of the MMA and AFA using a transarterial approach through the MMA (Figure 4A), and Onyx was injected to penetrate the DAVF and beginning of the draining vein (Figure 4B). Subsequently, angiography of the right internal carotid artery and external carotid artery showed complete embolization of the DAVF (Figure 4C-F). After the operation, the patient received conservative treatment for 10 days and was then discharged. At the half-year follow-up, the patient had recovered well without sequelae.

DISCUSSION

DAVF can occur anywhere in the venous sinuses and dura mater of the brain. However, it is relatively rare in the falcine sinus of the anterior cerebral falx because the falcine sinus is extremely rare in adults[2]. In addition, normally, the arterial supply to the anterior part of the cerebral falx is very small[6]. These arteries include the MMA, the AFA from the ophthalmic artery system, and the dural branches of the anterior cerebral arteries[7], which have high plasticity, as evidenced in moyamoya disease (Figure 5).

When necessary, these arteries are quite thick and strong, and the MMA can be connected to the posterior part of the AFA[5]. If the falcine sinus is not completely degraded, there is the potential for DAVF formation. According to current mainstream opinion, if the falcine sinus forms a thrombus and then communicates with the proliferative and dilated dural artery, DAVF formation can occur.

In cases of DAVF, the arteries near DAVF can be recruited to add to the feeding blood supply; there may be many or only a few arteries involved. For example, in case 1, only the dilated MMA was connected to the posterior part of the AFA as the blood supply. In contrast, in case 2, the blood supply was extensive. The bilateral ophthalmic arteries and the ends of the IMA were connected to the AFA through the anterior ethmoid artery, supplying blood to the DAVF, and the right MMA also supplied blood. The wide range of feeding arteries introduces large obstacles to DAVF treatment.

According to embryology, the anterior falcine sinus connects the superior and inferior sagittal sinuses, providing an alternative route for the cerebral venous drainage of the frontal lobes[2]. However, according to previous reports of DAVFs in the falcine sinus, the veins did not drain directly into the superior and inferior sagittal sinuses; instead, they drained through the cortical drainage veins in the medial side of the frontal lobe, forming Cognard type IV DAVFs. Although the falcine sinus may be open during DAVF formation, the falcine sinus does not communicate with the superior and inferior sagittal sinuses. Thus, DAVF formation can rely on cortical venous drainage only.

In case 1, only the cortical vein in the medial side of the frontal lobe was involved in drainage. In case 2, the deep vein system was also involved in drainage. Therefore, we can observe that venous drainage of the falcine sinus in cases of DAVF may be very extensive. Cognard type IV DAVFs in the falcine sinus are prone to rupture and hemorrhage.

Due to the location of the falcine sinus, interhemispheric hematomas form after rupture, which can break into the ventricle, as in both cases 1 and 2 reported in this paper. For DAVFs in the falcine sinus, similar to DAVFs located elsewhere, although various treatment options are available, EVT is still the most prevalent method. In addition, transarterial access is favored, unlike for DAVFs in the cavernous sinus, which allows the possibility of venous access for EVT[8].

For DAVF treatment by EVT, the MMA and the accessory meningeal artery are the gold standard vessels for EVT[9]. They also provide ideal routes to DAVFs in the falcine sinus. When choosing the MMA as the embolic route, the most important thing is to obtain the wedged position, which provides the ideal flow-arrest state for controlled delivery of embolic agents through the DAVF toward the venous side[10]. However, for DAVFs in the falcine sinus, it is very difficult for microcatheters to pass through the confluence of the MMA and the posterior part of AFA, which means that in our 2 cases, we were unable to achieve the ideal wedged position; we could use liquid embolic agents for EVT only at the location shown in Figures 2A and 3A.

Liquid embolic agents include n-butyl cyanoacrylate (NBCA, Histoacryl, Yocan Medical, Toronto, CA) and Onyx. NBCA has a better ability to penetrate the shunt. For example, Koyanagi *et al* successfully treated a DAVF in the falcine sinus with the help of NBCA through the MMA[5]. We also consider Onyx to be feasible because we do not need to worry about Onyx reflux in the MMA; Onyx will keep moving forward, and it is not difficult to remove microcatheters from the external carotid artery system. Thus, Onyx was used for treatment, with beneficial therapeutic effects.

CONCLUSION

Therefore, we believe that it is highly feasible to use Onyx for DAVFs in the falcine sinus using an arterial approach through the MMA to perform EVT. Nevertheless, due to the limited number of cases, we still need to accumulate additional experience.

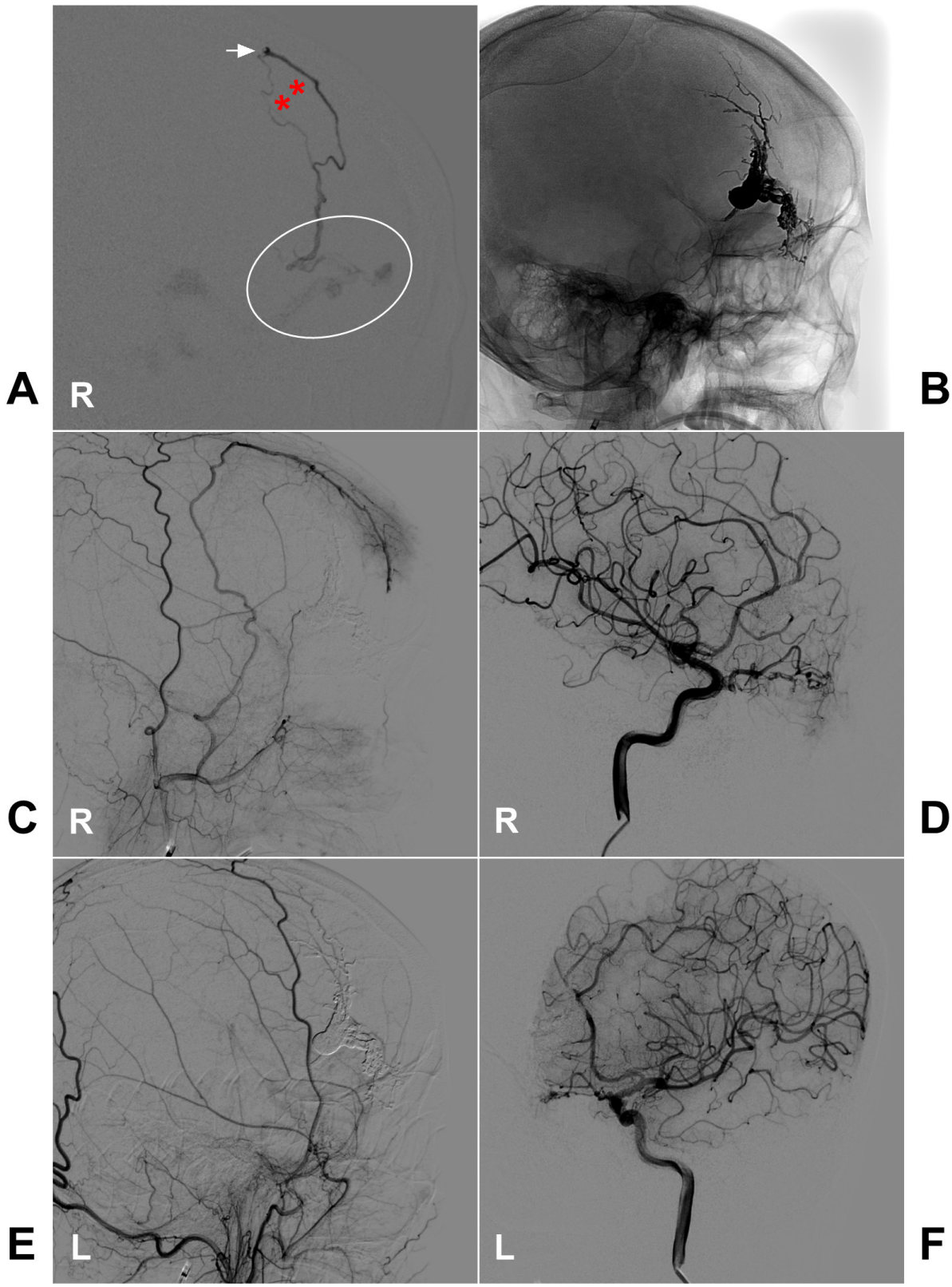

Figure 4: The EVT process in case 2

A: Microcatheter angiography of the right MMA showing the blood supply of the AFA (red asterisk). The arrow indicates the beginning of the AFA, which was also the position of the head end of the microcatheter. The ellipse denotes the DAVF. **B:** X-ray film showing Onyx casting in the DAVF via the MMA. **C-D**: Right ECA (C) and right ICA (D) showing complete DAVF embolization. **E-F**: Left ECA (E) and left ICA (F) showing complete DAVF embolization.

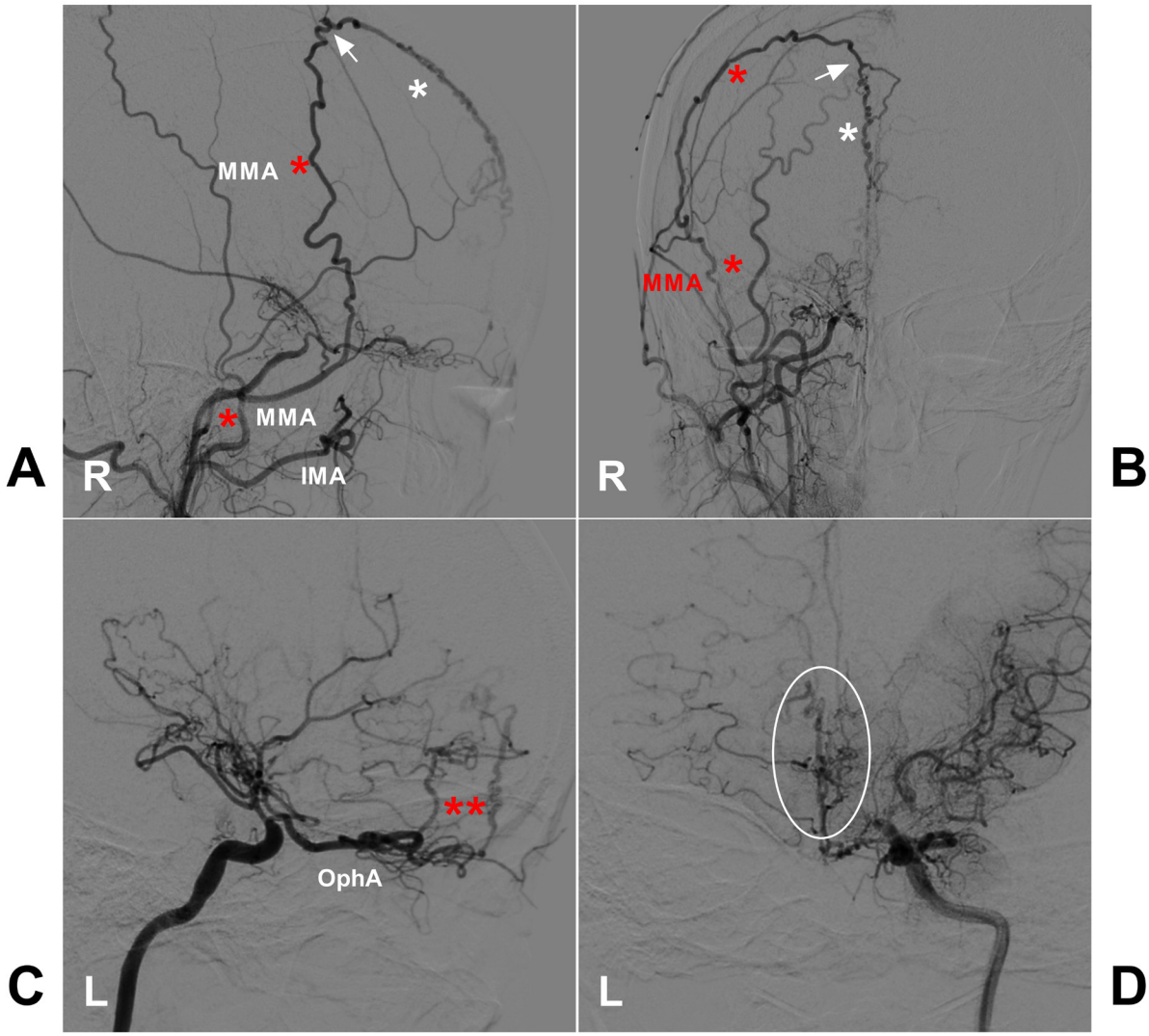

Figure 5: Potential arterial anastomosis inside the dura mater of the anterior part of the cerebral falx in a case of MMD
A-B: Right ECA angiography of the lateral position (A) and anterior position (B) showing that the MMA (red asterisk) coincides with the rear part of the AFA (white asterisk) at the midline (arrow). **C**: Left ICA angiography of the lateral position showing that the anterior ethmoidal artery from the OphA continues with the AFA (asterisks). **D**: Left ICA angiography of the anterior position showing the location of the AFA (ellipse).

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Jinlu Yu designed the study, Jinamin Piao collected the images and wrote the paper, and Zhongxi Yong collected the data.

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Case Report

Carotid artery myxoma: Case report and review of literature

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ABSTRACT

Myxomatous tumors of the carotid arteries are rare entities, especially when they present as an etiology for cerebral ischemia. We report a case of carotid artery myxoma culminating in a stroke in a young female patient without atherosclerotic risk factors.

A 39-year-old female with Sjogren Syndrome presented with right upper extremity weakness and dysarthria. Magnetic resonance imaging of the brain showed left parietal acute ischemic infarction. Carotid duplex revealed a significant left internal carotid artery stenosis, which corresponded to the magnetic resonance angiography findings. The patient underwent a left carotid endarterectomy. Intra-operatively, a gelatinous occlusive mass was found at the carotid bifurcation. Histopathological studies confirmed the diagnosis of myxoma. Further radiological investigations showed no residual tumor and no potential cardiac source of the tumor.

Carotid artery myxoma is a rare tumor and a rare etiology of stroke. Although exceptionally rare, carotid artery myxoma should be added to the list of uncommon differential diagnoses leading to carotid artery stenosis and cerebral ischemia.

KEY WORDS: carotid stenosis, cerebral ischemia, endarterectomy, myxoma, stroke

INTRODUCTION

Myxomas are benign tumors of mesenchymal origin with the capability of endothelial differentiation. They comprise the most common primary tumor of the heart, however, theoretically, these can arise within any endothelial surface and any blood vessel[1].

They can present with local obstruction and/or distal embolization, in addition to other non-specific systemic constitutional symptoms[2].

Upon review of the literature, there were no reported cases of a definite myxoma arising de novo from the carotid arteries. Instead, those cases were described as potential cardiac tumor emboli where the entire tumor embolized without any intracardiac residual[3,4]. We report the first definitive case of a myxoma arising from the carotid artery leading to an ipsilateral stroke.

CASE REPORT

A thirty-nine-year-old right-handed female presented with right upper extremity weakness and dysarthria. Symptoms resolved after 24 hours, and she denied any ataxia, visual impairment or diplopia, syncope, or drop attacks. There was no history of prior strokes, transient ischemic attacks, coronary artery disease, heart failure, arrhythmias, or cardiac valvular disease. She denied chest pain, palpitations or dyspnea. There was no history of neurological illness, and no prior seizures or migraines. No history of coagulopathy or thrombophilia in the patient or her family. Her past medical history is only significant for Sjogren's syndrome. The patient denied any history of smoking or alcohol consumption.

During her initial evaluation, her physical examination was only remarkable for several scattered unpigmented skin patches consistent with vitiligo without any other skin abnormalities. She was hemodynamically normal and afebrile. Neurological exam was grossly unremarkable with normal cranial nerve examination and intact power and sensory examinations of the upper and lower extremities bilaterally. Cardiac examination was also unremarkable

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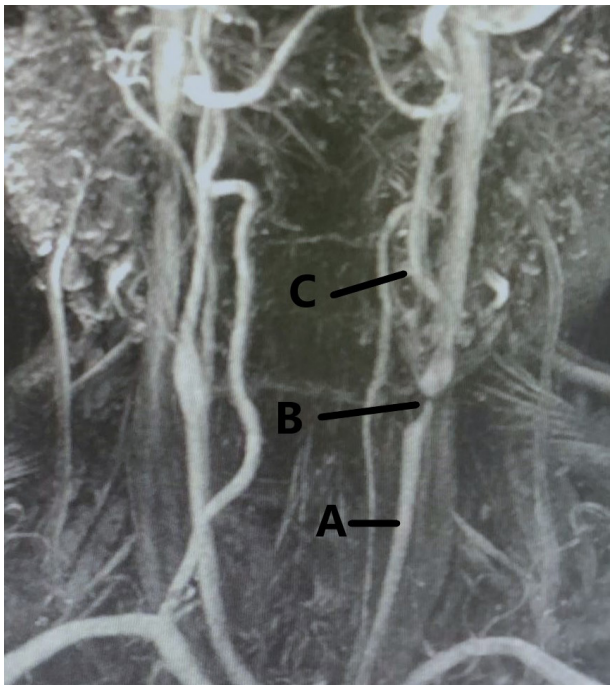

Figure 1: Magnetic resonance angiography of the carotid; A: left common carotid artery; B: carotid artery stenosis; C: distal internal carotid artery.

without additional sounds, murmurs or arrhythmias. The rest of the exam was unyielding.

Basic laboratory tests, chest xray, electrocardiogram and transthoracic echo were all within normal limits. Carotid duplex ultrasound measured raised peak systolic velocities in the left internal carotid artery consistent with 60-70% stenosis, and B-mode scan showed a hypoechoic plaque at the level of the carotid bifurcation. Magnetic resonance imaging (MRI) of the brain showed acute left parietal infarctions, and magnetic resonance angiography of the neck had consistent findings with the duplex ultrasound revealing a focal stenosis at the origin of the internal carotid artery (Figure 1) and without any other structural abnormalities.

The patient underwent a left carotid endarterectomy with patch angioplasty using bovine pericardium. The carotid was accessed using a retro-jugular approach and a shunt was used during clamping (Figures 2, 3). A gelatinous mass was found attached to the endothelium of the carotid bulb and was excised en mass with the endothelium during the endarterectomy (Figure 4). The patient tolerated the procedure well, had an uneventful postoperative course, and was discharged home the next day.

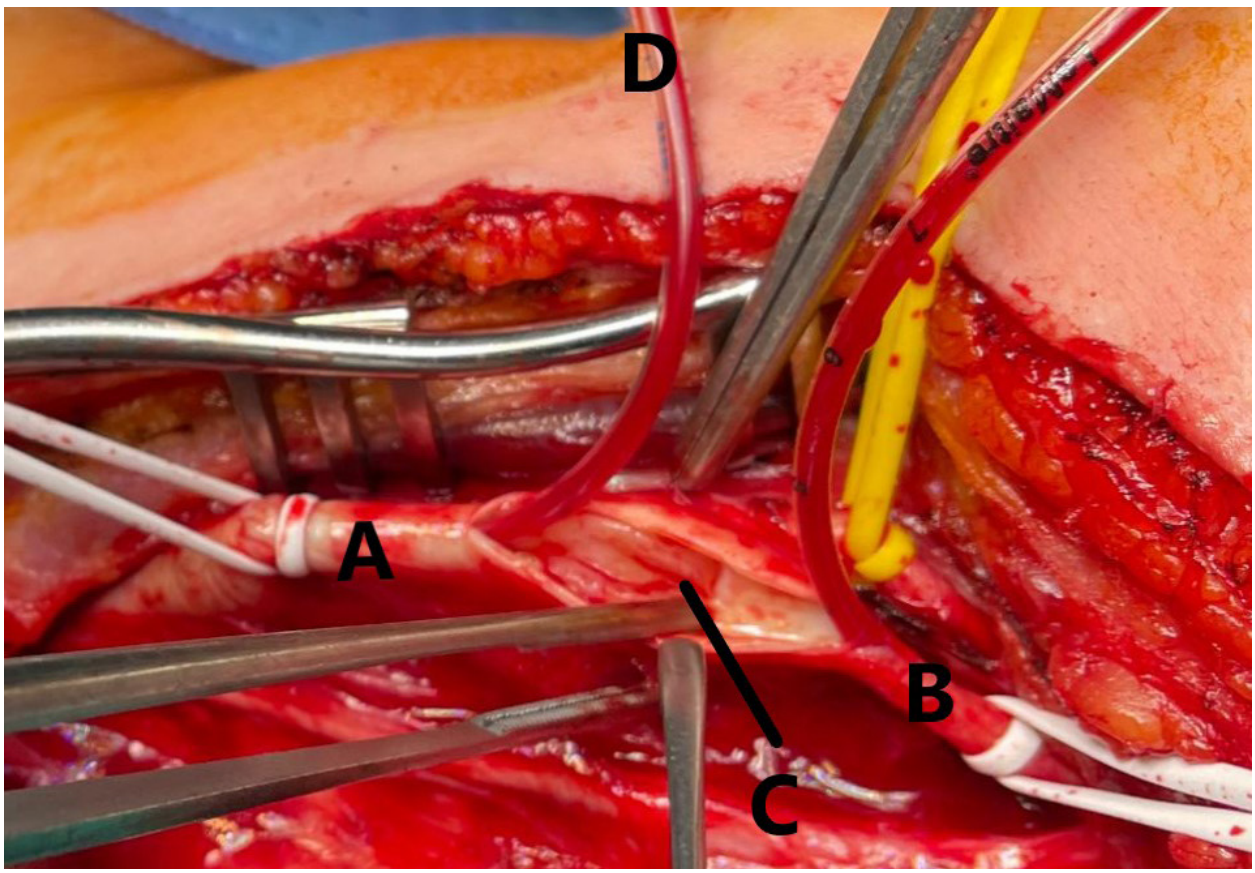

Figure 2: Intraoperative picture after carotid arteriotomy; A: Common carotid artery; B: Internal carotid artery; C: Myxoma occluding the carotid bulb; D: Inahara-Pruitt carotid Shunt.

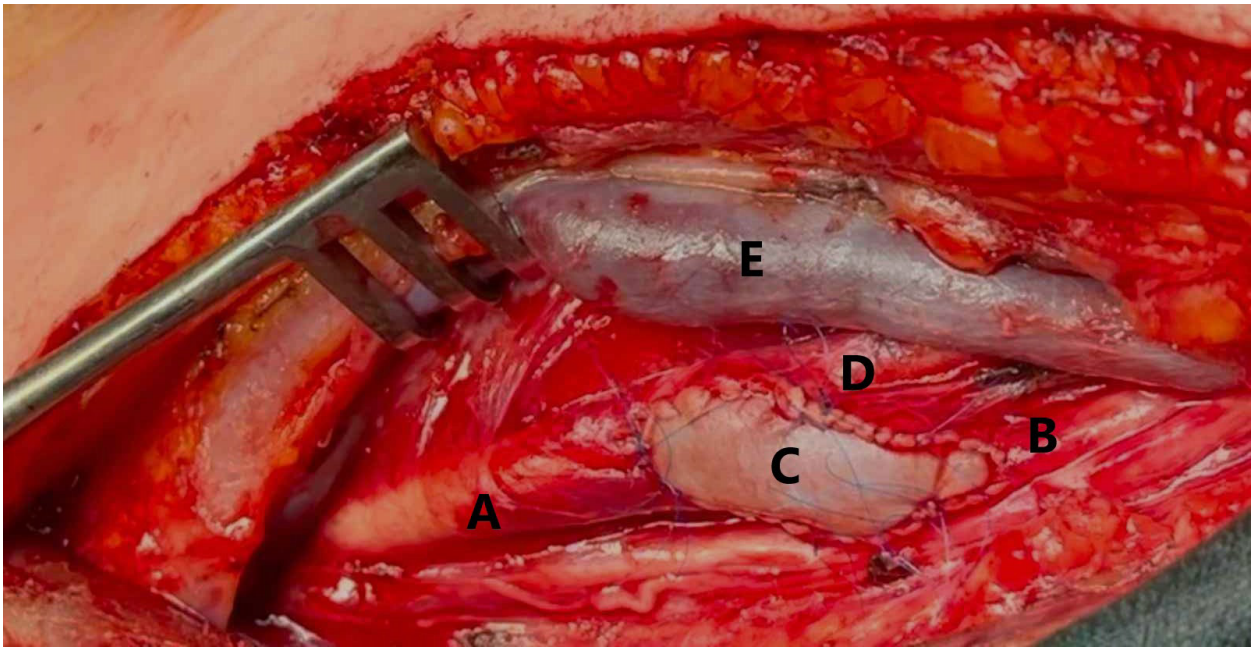

Figure 3: Closure of the carotid with pericardial Patch; A: Common carotid artery; B: Internal carotid artery; C: Pericardial Patch closure; D: External carotid artery; E: Internal Jugular vein.

Histopathology of the specimen confirmed the diagnosis of myxoma. Microscopic examination showed a lesion composed of blunt spindle cells surrounded by abundant myxoid stroma. The lesion was positive for CD 31, CD 34 and pan Keratin, as well as PAS/Alcian blue stain the myxoid background (Figure 5, 6). Cardiac imaging with an MRI ruled out a cardiac myxoma and any intra-cardiac thrombus. One month follow up carotid duplex showed patent carotids bilaterally with no evidence of stenosis.

DISCUSSION

Myxomas are benign tumors of mesenchymal origin with the ability to differentiate into endothelial and neural cell lines[1]. They produce vascular endothelial growth factor, leading to angiogenesis and tumor growth[5]. Histologically, scattered cells within an abundant mucopolysaccharide stroma are seen[1]. Macroscopically, these can be villous and friable, leading to embolization, or smooth and large, leading to locally obstructive phenomena[2].

Myxomas occur sporadically in the majority of patients. In a minority of patients, myxomas occur secondary to an inherited autosomal dominant disorder, Carney Complex. These patients have, in addition to early onset cardiac myxomas, extra-cardiac myxomas with a high recurrence risk, peripheral nerve schwannomas, skin pigmentation abnormalities, and

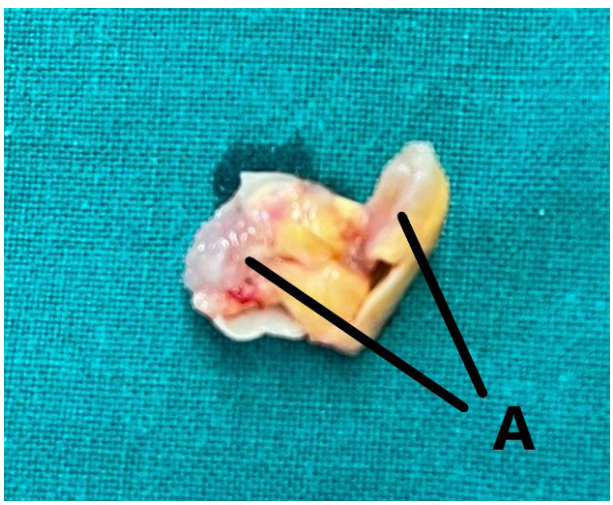

Figure 4: Myxoma excised from the carotid; A: Myxoma gelatinous material inside the carotid bulb and internal carotid artery.

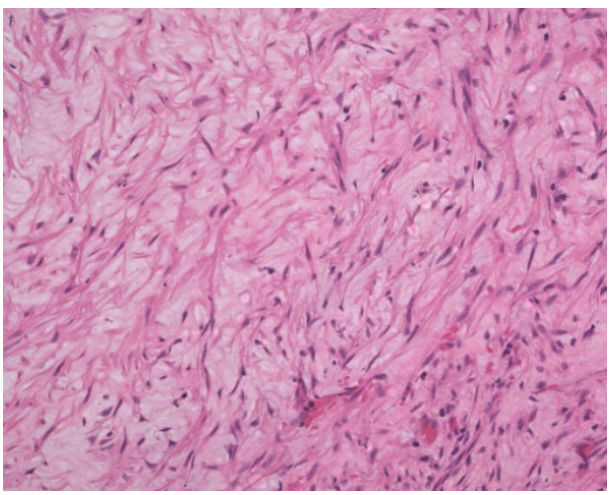

Figure 5: The histopathology of the myxoma, routine hematoxylin and eosin stain showing the spindle cells.

Table 1: Patient demographics and characteristics of reported carotid myxoma cases.

Findings	Alfawaz *et al*	Cortes-Vicente *et al* (4)	Robbin *et al* (3)
Age, year	39	37	41
Sex	Female	Female	Female
Co-morbidities	Sjögren Syndrome	None	Hypertension
Family history	Negative	Negative	Negative
Presentation	Stroke	Recurrent TIAs	Stroke
Carotid duplex	Stenosis of 60-70%	Stenosis ≥ 70%.	Short segment occlusion
Carotid MRA	Yes	Yes	No
Carotid angiography	No	No	Yes
CT brain	No	No	Yes
MRI brain	Yes	Yes	No
Cardiac MRI	No cardiac myxoma	No cardiac myxoma	No cardiac myxoma
Echocardiography	Normal	Normal	Normal
Management	Left carotid endarterectomy	Intra-arterial excision, carotid left intact	En. bloc removal of artery with tumor
Morphology	Gelatinous, soft mass	Reddish gelatinous mass	Gelatinous mass, without wall invasion
Histopathology	Myxoma	Myxoma	Myxoma
Follow up carotid duplex	Normal	Normal	Normal

CT: computed tomography; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; TIA: transient ischaemic attack

various endocrine tumors[6]. Although our patient did have a skin pigmentation anomaly, vitiligo, this was not consistent with the reported features of Carney complex, where patients have unusual ephelides (freckles), pigmented lentigines and blue nevi.

Most of the reported myxomas leading to cerebral ischemia occur after embolization of a cardiac tumor to the carotid arteries and terminal branches. These most commonly occur in the left atrium leading to systemic emboli, however, right atrial myxomas do occur and only lead to pulmonary emboli, unless there is a right to left shunt[1,2,7,8]. A literature review yielded two other reported cases of carotid myxomas, and their findings are summarized in Table 1[3,4]. Although a search for a primary cardiac tumor was unavailing in both of the reported cases, the authors commented on the possibility of a completely embolized cardiac tumor lodging within the carotid artery. We feel that our case is different given the pathology findings showing the tumor embedded with the arterial endothelial wall and removal with endarterectomy as opposed to local mass excision or shelling out of the tumor itself in the first case. The second case was managed with en-bloc resection of the carotid artery, but the pathology did not reveal any arterial wall extension of the mass. Due to the rarity of this pathology, there is no consensus on typical histological features of a primary carotid myxoma over cardiac embolization. We suggest that endothelial involvement of the tumor, an absence of a cardiac myxoma, and absence of thrombus within the carotid (which would occur with any acute embolic etiology) favor a primary carotid myxoma over a complete cardiac myxoma embolization.

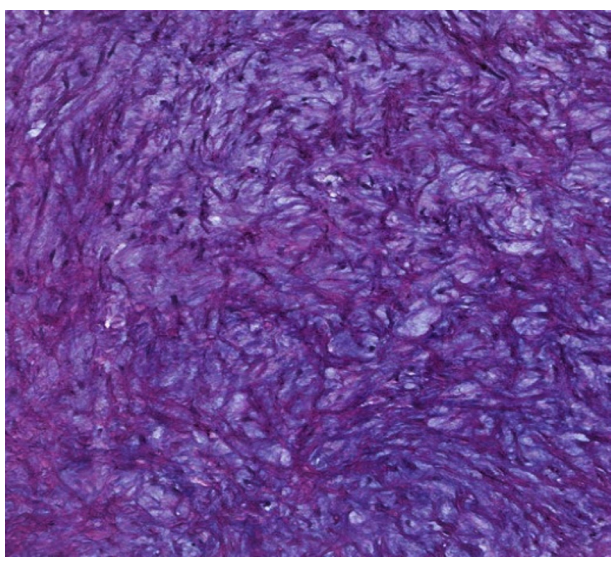

Figure 6: The histopathology of the myxoma, PAS and alcian blue stain highlighting the myxoid background.

Gadolinium-enhanced MRI is highly sensitive for the detection of cardiac myxomas[9]. Gulati *et al* compared contrast enhanced MRI and transthoracic echo (TTE) in 28 patients with suspected intracardiac masses. MRI was more likely to be technically optimal (100% vs 82%) and suggest a diagnosis (75% vs 29%), and less likely to miss a mass (0 vs 2 patients). The authors concluded that MRI was advantageous over TTE (even with the addition of transesophageal echo)[10]. Our patient underwent a TTE pre-operatively as a part of her ischemic stroke work-up and pre-operative to cardiac risk assessment. She then underwent a contrast enhanced MRI post-operatively, both of which did not reveal any evidence of a primary intracardiac myxoma.

CONCLUSION

Carotid artery myxoma is a rare tumor and a rare etiology of stroke. Prior to making that diagnosis, the presence of such a tumor within the carotid

lumen, most commonly identified due to its acutely symptomatic nature, should trigger a search for a primary cardiac tumor that led to cerebrovascular embolization.

Although exceptionally rare, carotid artery myxoma should be added to the list of uncommon differential diagnoses leading to carotid artery stenosis and cerebral ischemia.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2024; 56 (1): 74 - 76

Prevalence of overactive bladder among overweight and obese women: A prospective cross-sectional cohort study

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Eur J Obstet Gynecol Reprod Biol. 2024 Feb 6:295:59-64. doi: 10.1016/j.ejogrb.2024.02.010. Online ahead of print.

OBJECTIVE

To evaluate the effect of body mass index (BMI) on the prevalence of overactive bladder syndrome (OAB), severity of symptoms, and quality of life in affected patients.

METHODS

We conducted a prospective cross-sectional study of 1351 consecutive patients who were recruited between June 2021 and May 2022. Patients were divided according to BMI (normal: <25.0, overweight: 25-29.9, obese: ≥30) and menopausal status. The latter were divided according to the presence or absence of urinary incontinence in the normal, wet-OAB and dry-OAB groups. A validated questionnaire, the International Consultation on Incontinence Questionnaire in Overactive Bladder (ICIQ-OAB), in the English and Arabic languages was used.

RESULTS

A total of 1351 patients were included. For women who were overweight, there was a greater prevalence of dry-OAB ($p = 0.02$), However, the prevalence of both dry and wet-OAB were higher in obese women ($p < 0.00001$). Compared to women with a normal BMI, women who were overweight or obese had a greater likelihood of developing abnormal daytime urine frequency and nocturia, with p values ≤ 0.01. The ORs of overweight and obese women were 3.1 and 5.3, respectively, for experiencing wet OAB in comparison to women with a normal BMI. Additionally, the odds of developing severe OAB in overweight and obese women were 5.8 and 18.6, respectively, which negatively affects their quality of life (QoL).

CONCLUSION

The risk of developing OAB symptomatology is significantly greater in overweight and obese patients. As BMI increases, the symptomatology, perceived discomfort and QoL of patients with OAB worsen.

Acute Respiratory Distress Syndrome in a Patient With Systemic Sclerosis: A Case of a Life-Threatening Complication

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Cureus. 2024 Jan 10;16(1):e52003. doi: 10.7759/cureus.52003. eCollection 2024 Jan.

Numerous pulmonary conditions, such as aspiration pneumonia and acute respiratory distress syndrome (ARDS), may result from aspiration of gastric or oropharyngeal contents passing into the lower respiratory tract. ARDS is a type of diffuse lung injury that is distinguished by the abrupt onset of extensive pulmonary inflammation accompanied by the failure of multiple organ systems. Systemic sclerosis is an uncommon connective tissue disorder that presents with skin thickening, the etiology of which remains unknown. Esophageal luminal dilatation is observed in the distal third of the esophagus in most cases of systemic sclerosis. This dilatation is primarily attributed to the greater abundance of smooth muscle fibers in this area. Here, we present the case of a 70-year-old female patient who was diagnosed clinically with diffuse systemic sclerosis and fulfilled the 2013 European League Against Rheumatism/American College of Rheumatology classification criteria. She had esophageal dilatation, with an esophageal luminal diameter measured at the upper, middle, and lower thoracic esophagus of 2.5 cm, 2.5 cm, and 3.5 cm, respectively. The patient was admitted to the intensive care unit (ICU) due to ARDS from aspiration pneumonia. Our patient's complicated condition at the time of ICU admission with ARDS secondary to aspiration pneumonia was primarily due to esophageal dilatation and reflux. Aggressive anti-reflux pharmacotherapy and bed elevation may be beneficial in preventing pulmonary injury caused by aspiration. Esophageal complications are common in such patients and can have a substantial impact on the prognosis and quality of life. Regular medical attention is necessary to identify and manage any potential issues.

Perforated Ischemic Ulcer at the Jejuno-Jejunal Anastomosis 9 Years Post-laparoscopic Roux-en-Y Gastric Bypass-a Case Report

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Obes Surg. 2024 Feb 13. doi: 10.1007/s6-07088-024-11695. Online ahead of print.

BACKGROUND
Obesity is a common disease among Kuwaitis. Multiple types of bariatric procedures are offered in Kuwait. R-Y gastric bypass is among the common surgeries performed. Early and late complications must be recognized as early as possible to avoid undesirable consequences.

CASE PRESENTATION
Here, we present a case of a 48-year-old lady presented as acute abdominal pain and diagnosed as Jejuno-Jejunal anastomosis site ulceration / perforation taking place several years from surgery.

DISCUSSION
Etiology of late perforation can be attributed to ischemia. Computerized tomography (C.T.) scan is the gold standard for diagnosis. Management can be laparoscopic or open surgery depending on surgeon expertise. We performed a laparoscopic resection for the extended perforated jejunal recess and that was enough to resolve our patient's problem.

Secretome analysis and virulence assessment in *Abiotrophia defectiva*

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[2]Department of General Dental Practice, College of Dentistry, Kuwait University, Safat, Kuwait.

J Oral Microbiol. 2024 Feb 12;16(1):2307067. doi: 20002297.2024.2307067/10.1080. eCollection 2024.

BACKGROUND
Abiotrophia defectiva, although infrequently occurring, is a notable cause of culture-negative infective endocarditis with limited research on its virulence. Associated with oral infections such as dental caries, exploring its secretome may provide insights into virulence mechanisms. Our study aimed to analyze and characterize the secretome of A. defectiva strain CCUG 27639.

METHODS
Secretome of A. defectiva was prepared from broth cultures and subjected to mass spectrometry and proteomics for protein identification. Inflammatory potential of the secretome was assessed by ELISA.

RESULTS
Eighty-four proteins were identified, with diverse subcellular localizations predicted by PSORTb. Notably, 20 were cytoplasmic, 12 cytoplasmic membrane, 5 extracellular, and 9 cell wall-anchored proteins. Bioinformatics tools revealed 54 proteins secreted via the 'Sec' pathway and 8 via a non-classical pathway. Moonlighting functions were found in 23 proteins, with over 20 exhibiting potential virulence properties, including peroxiredoxin and oligopeptide ABC transporter substrate-binding protein. Gene Ontology and KEGG analyses categorized protein sequences in various pathways. STRING analysis revealed functional protein association networks. Cytokine profiling demonstrated significant proinflammatory cytokine release (IL-8, IL-1β, and CCL5) from human PBMCs.

CONCLUSIONS
Our study provides a comprehensive understanding of A. defectiva's secretome, laying the foundation for insights into its pathogenicity.

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Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2024; 56 (1): 77 - 85

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WHO-Facts Sheet

1. Headache disorders
2. Lymphatic filariasis
3. Mycotoxins
4. Physical activity
5. Schizophrenia

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1. Headache disorders

KEY FACTS

- Headache disorders are among the most common disorders of the nervous system.
- It has been estimated that almost half of the adult population have had a headache at least once within the last year.
- Headache disorders, which are characterized by recurrent headache, are associated with personal and societal burdens of pain, disability, damaged quality of life, and financial cost.
- Worldwide, a minority of people with headache disorders are diagnosed appropriately by a health-care provider.
- Headache has been underestimated, under-recognized and under-treated throughout the world.

What are headache disorders?

Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Headache itself is a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache. Headache can also be caused by or occur secondarily to a long list of other conditions, the most common of which is medication-overuse headache.

How common are headache disorders?

Globally, it has been estimated that prevalence among adults of current headache disorder (symptomatic at least once within the last year) is about 50%. Half to three quarters of adults aged 18–65 years in the world have had headache in the last year and, among those individuals, 30% or more have reported migraine. Headache on 15 or more days every month affects 1.7–4% of the world's adult population. Despite regional variations, headache disorders are a worldwide problem, affecting people of all ages, races, income levels and geographical areas.

What is the burden due to headache disorders?

Not only is headache painful, but it is also disabling. In the Global Burden of Disease Study, updated in 2013, migraine on its own was found to be the sixth highest cause worldwide of years lost due to disability (YLD). Headache disorders collectively were third highest.

Headache disorders impose a recognizable burden on sufferers including sometimes substantial personal suffering, impaired quality of life and financial cost. Repeated headache attacks, and often the constant fear of the next one, damage family life, social life and employment. The long-term effort of coping with a chronic headache disorder may also predispose the individual to other illnesses. For example, anxiety and depression are significantly more common in people with migraine than in healthy individuals.

Types of headache disorders

Migraine, tension-type headache and medication-overuse headache are of public health importance since they are responsible for high population levels of disability and ill-health.

Migraine

- A primary headache disorder.
- Migraine most often begins at puberty and most affects those aged between 35 and 45 years.
- It is more common in women, usually by a factor of about 2:1, because of hormonal influences.
- It is caused by the activation of a mechanism deep in the brain that leads to release of pain-producing

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inflammatory substances around the nerves and blood vessels of the head.
- Migraine is recurrent, often life-long, and characterized by recurring attacks.
- Attacks typically include:
  - headache, which is:
    - of moderate or severe intensity
    - one-sided
    - pulsating in quality
    - aggravated by routine physical activity
    - with duration of hours to 2-3 days
  - nausea (the most characteristic associated feature);
  - attack frequency is anywhere between once a year and once a week; and
  - in children, attacks tend to be of shorter duration and abdominal symptoms more prominent.

Tension-type headache (TTH)
- TTH is the most common primary headache disorder.
- Episodic TTH, occurring on fewer than 15 days per month, is reported by more than 70% of some populations.
- Chronic TTH, occurring on more than 15 days per month, affects 1-3% of adults.
- TTH often begins during the teenage years, affecting three women to every two men.
- Its mechanism may be stress-related or associated with musculoskeletal problems in the neck.
- Episodic TTH attacks usually last a few hours, but can persist for several days.
- Chronic TTH can be unremitting and is much more disabling than episodic TTH.
- This headache is described as pressure or tightness, often like a band around the head, sometimes spreading into or from the neck.

Cluster Headache (CH)
- A primary headache disorder.
- CH is relatively uncommon affecting fewer than 1 in 1000 adults, affecting six men to each woman.
- Most people developing CH are in their 20s or older.
- It is characterized by frequently recurring (up to several times a day), brief but extremely severe headache, usually focused in or around one eye, with tearing and redness of the eye, the nose runs or is blocked on the affected side and the eyelid may droop.
- CH has episodic and chronic forms.

Medication-overuse headache (MOH)
- MOH is caused by chronic and excessive use of medication to treat headache.
- MOH is the most common secondary headache disorder.
- It may affect up to 5% of some populations, women more than men.
- MOH occurs by definition on more days than not, is oppressive, persistent and often at its worst on awakening.

Social and economic burden of headache

Headache disorders are a public-health concern given the associated disability and financial costs to society. As headache disorders are most troublesome in the productive years (late teens to 50s), estimates of their financial cost to society – principally from lost working hours and reduced productivity – are massive. In the United Kingdom, for example, some 25 million working- or school-days are lost every year because of migraine alone; this financial cost may be matched by TTH and MOH combined. Headache is high among causes of consulting medical practitioners: one-third of all neurological consultations were for headache, in one survey.

Yet, many of those troubled by headache do not receive effective care. For example, in the United States of America and the United Kingdom, only half of those identified with migraine had seen a doctor for headache-related reasons in the previous 12 months, and only two-thirds had been correctly diagnosed. Most were solely reliant on over-the-counter medications.

Treatment

Appropriate treatment of headache disorders requires training of health professionals, accurate diagnosis and recognition of the conditions, appropriate treatment with cost-effective medications, simple lifestyle modifications, and patient education. The main classes of drugs to treat headache disorders include: analgesics, anti-emetics, specific anti-migraine medications, and prophylactic medications.

Barriers to effective care

Lack of knowledge among health-care providers is the principal clinical barrier. Worldwide, on average, only 4 hours of undergraduate medical education are dedicated to instruction on headache disorders. A large number of people with headache disorders are not diagnosed and treated: worldwide only 40% of those with migraine or TTH are professionally diagnosed, and only 10% of those with MOH.

Poor awareness extends to the general public. Headache disorders are not perceived by the public as serious since they are mostly episodic, do not cause death, and are not contagious. The low consultation rates in developed countries may indicate that many affected people are unaware that effective

treatments exist. Half of people with headache disorders are estimated to be self-treating.

Many governments, seeking to constrain health-care costs, do not acknowledge the substantial burden of headache on society. They might not recognize that the direct costs of treating headache are small in comparison with the huge indirect-cost savings that might be made (eg, by reducing lost working days) if resources were allocated to treat headache disorders appropriately.

WHO response

These evident burdens call for action. WHO recognizes this, and is a partner, with the non-governmental organization Lifting The Burden, in the Global Campaign against Headache. This initiative commenced in 2004 and aims not only to raise awareness of headache disorders but also to improve the quality of headache care and access to it worldwide. WHO published the Atlas of headache disorders in 2011, describing the burden due to headache disorders and resources available to reduce them.

2. Lymphatic filariasis

KEY FACTS

- Lymphatic filariasis impairs the lymphatic system and can lead to the abnormal enlargement of body parts, causing pain, severe disability and social stigma.
- Over 882 million people in 44 countries worldwide remain threatened by lymphatic filariasis and require preventive chemotherapy to stop the spread of this parasitic infection.
- Lymphatic filariasis can be eliminated by stopping the spread of infection through preventive chemotherapy with safe medicine combinations repeated annually. More than 9 billion cumulative treatments have been delivered to stop the spread of infection since 2000.
- As of 2018, 51 million people were infected – a 74% decline since the start of WHO's Global Programme to Eliminate Lymphatic Filariasis in 2000.
- Due to successful implementation of WHO strategies, 740 million people no longer require preventive chemotherapy.
- An essential, recommended package of care can alleviate suffering and prevent further disability among people living with disease caused by lymphatic filariasis.

Overview

Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. Infection occurs when filarial parasites are transmitted to humans through mosquitoes. Infection is usually acquired in childhood and causes hidden damage to the lymphatic system.

The painful and profoundly disfiguring visible manifestations of the disease – lymphoedema, elephantiasis and scrotal swelling – occur later in life and can lead to permanent disability. These patients are not only physically disabled, but suffer mental, social and financial losses contributing to stigma and poverty.

In 2021, 882.5 million people in 44 countries were living in areas that require preventive chemotherapy to stop the spread of infection.

The global baseline estimate of people affected by lymphatic filariasis was 25 million men with hydrocele and over 15 million people with lymphoedema. At least 36 million people remain with these chronic disease manifestations. Eliminating lymphatic filariasis can prevent unnecessary suffering and contribute to the reduction of poverty.

Cause and transmission

Lymphatic filariasis is caused by infection with parasites classified as nematodes (roundworms) of the family Filariodidea. There are 3 types of these thread-like filarial worms:

- *Wuchereria bancrofti*, which is responsible for 90% of the cases
- *Brugia malayi*, which causes most of the remainder of the cases
- *Brugia timori*, which also causes the disease.

Adult worms nest in the lymphatic vessels and disrupt the normal function of the lymphatic system. The worms can live for approximately 6–8 years and, during their lifetime, produce millions of microfilariae (immature larvae) that circulate in the blood.

Mosquitoes are infected with microfilariae by ingesting blood when biting an infected host. Microfilariae mature into infective larvae within the mosquito. When infected mosquitoes bite people, mature parasite larvae are deposited on the skin, from where they can enter the body. The larvae then migrate to the lymphatic vessels where they develop into adult worms, thus continuing a cycle of transmission.

Lymphatic filariasis is transmitted by different types of mosquitoes, for example by the *Culex* mosquito, widespread across urban and semi-urban areas, *Anopheles*, mainly found in rural areas, and *Aedes*, mainly in endemic islands in the Pacific.

Symptoms

Lymphatic filariasis infection involves asymptomatic, acute and chronic conditions. The majority of infections are asymptomatic, showing

no external signs of infection while contributing the transmission of the parasite. These asymptomatic infections still cause damage to the lymphatic system and the kidneys and alter the body's immune system.

When lymphatic filariasis develops into chronic conditions it leads to lymphoedema (tissue swelling) or elephantiasis (skin/tissue thickening) of limbs and hydrocele (scrotal swelling). Involvement of breasts and genital organs is common. Such body deformities often lead to social stigma and sub-optimal mental health, loss of income-earning opportunities and increased medical expenses for patients and their caretakers. The socioeconomic burdens of isolation and poverty are immense.

Acute episodes of local inflammation involving skin, lymph nodes and lymphatic vessels often accompany chronic lymphoedema or elephantiasis. Some of these episodes are caused by the body's immune response to the parasite. Most are the result of secondary bacterial skin infection where normal defenses have been partially lost due to underlying lymphatic damage. These acute attacks are debilitating, may last for weeks and are the primary cause of lost wages among people suffering with lymphatic filariasis.

Treatment

Elimination of lymphatic filariasis is possible by stopping the spread of the infection through preventive chemotherapy. The WHO-recommended preventive chemotherapy strategy for lymphatic filariasis elimination is mass drug administration (MDA). MDA involves administering an annual dose of medicines to the entire at-risk population. The medicines used have a limited effect on adult parasites but effectively reduce the density of microfilariae in the bloodstream and prevent the spread of parasites to mosquitoes.

The MDA regimen recommended depends on the co-endemicity of lymphatic filariasis with other filarial diseases. WHO recommends the following MDA regimens:

- albendazole (400 mg) alone twice per year for areas co-endemic with loiasis;
- ivermectin (200 mcg/kg) with albendazole (400 mg) in countries with onchocerciasis;
- diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in countries without onchocerciasis; and
- ivermectin (200 mcg/kg) together with diethylcarbamazine citrate (DEC) (6 mg/kg) and albendazole (400 mg) in countries without onchocerciasis and where other programmatic conditions are met.

The impact of MDA depends on the efficacy of the regimen and the coverage (proportion of total population ingesting the medicines). MDA with the 2-medicine regimens have interrupted the transmission cycle when conducted annually for at least 4–6 years with effective coverage of the total population at risk. Salt fortified with DEC has also been used in a few unique settings to interrupt the transmission cycle.

At the start of GPELF, 81 countries were considered endemic for lymphatic filariasis. Further epidemiological data reviewed since, indicate that preventive chemotherapy was not required in 10 countries. From 2000 to 2021, 9 billion cumulative treatments were delivered to more than 935 million people at least once in 70 countries, considerably reducing transmission in many places. The population requiring MDA has declined by 52% (740 million) where infection prevalence has been reduced below elimination thresholds. The overall economic benefit of the programme during 2000–2007 is conservatively estimated at US$ 24 billion. Treatments until 2015 are estimated to have averted at least US$ 100.5 billion of economic loss expected to have occurred over the lifetime of cohorts who have benefited from treatment.

Seventeen countries and territories (Cambodia, the Cook Islands, Egypt, Kiribati, Maldives, Malawi, Marshall Islands, Niue, Palau, Sri Lanka, Thailand, Togo, Tonga, Vanuatu, Viet Nam, Wallis and Futuna, and Yemen) are now acknowledged as achieving elimination of lymphatic filariasis as a public health problem. By 2021, 11 countries had successfully implemented recommended strategies, stopped large-scale treatment and are under surveillance to demonstrate that elimination has been achieved. Preventive chemotherapy is still required in 44 countries and within 9 of these countries MDA has not yet been delivered to all endemic areas as of the end of 2021.

Morbidity management

Morbidity management and disability prevention are vital for improving public health and are essential services that should be provided by the health care system to ensure sustainability. Surgery can alleviate most cases of hydrocele. Clinical severity and progression of the disease, including acute inflammatory episodes, can be reduced and prevented with simple measures of hygiene, skin care, exercises and elevation of affected limbs. People with lymphoedema must have access to continuing care throughout their lives, both to manage the disease and to prevent progression to more advanced stages.

The GPELF aims to provide access to an essential package of care for every person with associated chronic manifestations of lymphatic filariasis in all

areas where the disease is present, thus alleviating suffering and promoting improvement in their quality of life.

Goals toward the elimination of lymphatic filariasis will be achieved if affected people have access to the following essential package of care:

- treatment for episodes of adenolymphangitis (ADL);
- guidance in applying simple measures to manage lymphoedema to prevent progression of disease and debilitating, inflammatory episodes of ADL;
- surgery for hydrocele; and
- treatment for infection.

Vector control

Mosquito control is a supplemental strategy supported by WHO. It is used to reduce transmission of lymphatic filariasis and other mosquito-borne infections. Depending on the parasite-vector species, measures such as insecticide-treated nets, indoor residual spraying or personal protection measures may help protect people from infection. The use of insecticide-treated nets in areas where *Anopheles* is the primary vector for filariasis enhances the impact on transmission during and after MDA. Historically, vector control has in select settings contributed to the elimination of lymphatic filariasis in the absence of large-scale preventive chemotherapy.

WHO response

World Health Assembly resolution WHA50.29 encourages Member States to eliminate lymphatic filariasis as a public health problem. In response, WHO launched its Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000.

WHO's strategy is based on 2 key components:

- stopping the spread of infection through large-scale annual treatment of all eligible people in an area or region where infection is present; and
- alleviating the suffering caused by lymphatic filariasis through provision of the recommended essential package of care.

In 2020, GPELF set the following goals for the new NTD Road Map (2021–2030):

- 58 (80%) endemic countries have met the criteria for validation of elimination of lymphatic filariasis as a public health problem, with both sustained infection rates below target thresholds for at least 4 years after stopping MDA and providing the essential package of care in all areas with known patients;
- 72 (100%) endemic countries implement post-MDA or post-validation surveillance; and
- reduction to 0 of the total population requiring MDA.

3. Mycotoxins

KEY FACTS

- Mycotoxins are naturally occurring toxins produced by certain moulds (fungi) and can be found in food.
- The moulds grow on a variety of different crops and foodstuffs including cereals, nuts, spices, dried fruits, apples and coffee beans, often under warm and humid conditions.
- Mycotoxins can cause a variety of adverse health effects and pose a serious health threat to both humans and livestock.
- The adverse health effects of mycotoxins range from acute poisoning to long-term effects such as immune deficiency and cancer.
- A scientific expert committee jointly convened by WHO and the Food and Agriculture Organization of the United Nations (FAO) – called JECFA – is the international body responsible for evaluating the health risk from natural toxins including mycotoxins.
- International standards and codes of practice to limit exposure to mycotoxins from certain foods are established by the Codex Alimentarius Commission based on JECFA assessments.

Overview

Mycotoxins are toxic compounds that are naturally produced by certain types of moulds (fungi). Moulds that can produce mycotoxins grow on numerous foodstuffs such as cereals, dried fruits, nuts and spices. Mould growth can occur either before harvest or after harvest, during storage, on/in the food itself often under warm, damp and humid conditions. Most mycotoxins are chemically stable and survive food processing.

Several hundred different mycotoxins have been identified, but the most commonly observed mycotoxins that present a concern to human health and livestock include aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone and nivalenol/deoxynivalenol. Mycotoxins appear in the food chain as a result of mould infection of crops both before and after harvest. Exposure to mycotoxins can happen either directly by eating infected food or indirectly from animals that are fed contaminated feed, in particular from milk.

Mycotoxins commonly found in food

The effects of some food-borne mycotoxins are acute with symptoms of severe illness appearing quickly after consumption of food products contaminated with mycotoxins. Other mycotoxins occurring in food have been linked to long-term effects on health, including

the induction of cancers and immune deficiency. Of the several hundred mycotoxins identified so far, about a dozen have gained the most attention due to their severe effects on human health and their occurrences in food.

Aflatoxins are amongst the most poisonous mycotoxins and are produced by certain moulds (*Aspergillus flavus* and *Aspergillus parasiticus*) which grow in soil, decaying vegetation, hay, and grains. Crops that are frequently affected by *Aspergillus* spp. include cereals (corn, sorghum, wheat and rice), oilseeds (soybean, peanut, sunflower and cotton seeds), spices (chili peppers, black pepper, coriander, turmeric and ginger) and tree nuts (pistachio, almond, walnut, coconut and Brazil nut). The toxins can also be found in the milk of animals that are fed contaminated feed, in the form of aflatoxin M1. Large doses of aflatoxins can lead to acute poisoning (aflatoxicosis) and can be life threatening, usually through damage to the liver. Aflatoxins have also been shown to be genotoxic, meaning they can damage DNA and cause cancer in animal species. There is also evidence that they can cause liver cancer in humans.

Ochratoxin A is produced by several species of *Aspergillus* and *Penicillium* and is a common food-contaminating mycotoxin. Contamination of food commodities, such as cereals and cereal products, coffee beans, dry vine fruits, wine and grape juice, spices and liquorice, occurs worldwide. Ochratoxin A is formed during the storage of crops and is known to cause a number of toxic effects in animal species. The most sensitive and notable effect is kidney damage, but the toxin may also have effects on fetal development and on the immune system. Contrary to the clear evidence of kidney toxicity and kidney cancer due to ochratoxin A exposure in animals, this association in humans is unclear, however effects on kidney have been demonstrated.

Patulin is a mycotoxin produced by a variety of moulds, particularly Aspergillus, Penicillium and Byssochlamys. Often found in rotting apples and apple products, patulin can also occur in various mouldy fruits, grains and other foods. Major human dietary sources of patulin are apples and apple juice made from affected fruit. The acute symptoms in animals include liver, spleen and kidney damage and toxicity to the immune system. For humans, nausea, gastrointestinal disturbances and vomiting have been reported. Patulin is considered to be genotoxic however a carcinogenic potential has not been demonstrated yet.

Fusarium fungi are common to the soil and produce a range of different toxins, including trichothecenes such as deoxynivalenol (DON), nivalenol (NIV) and T-2 and HT-2 toxins, as well as zearalenone (ZEN) and fumonisins. The formation of the moulds and toxins occur on a variety of different cereal crops. Different fusarium toxins are associated with certain types of cereal. For example, both DON and ZEN are often associated with wheat, T-2 and HT-2 toxins with oats, and fumonisins with maize (corn). Trichothecenes can be acutely toxic to humans, causing rapid irritation to the skin or intestinal mucosa and lead to diarrhoea. Reported chronic effects in animals include suppression of the immune system. ZEN has been shown to have hormonal, estrogenic effects and can cause infertility at high intake levels, particularly in pigs. Fumonisins have been related to oesophageal cancer in humans, and to liver and kidney toxicity in animals.

Reducing risk

It is important to note that mould that produces mycotoxins can grow on a variety of different crops and foodstuff and can penetrate deep into food and do not just grow on the surface. Mould usually does not grow in properly dried and stored foods, so efficient drying of commodities and maintenance of the dry state, or proper storage, is an effective measure against mould growth and the production of mycotoxins.

To minimize the health risk from mycotoxins, people are advised to:

- inspect whole grains (especially corn, sorghum, wheat, rice), dried figs and nuts such as peanuts, pistachio, almond, walnut, coconut, Brazil nuts and hazelnuts which are all regularly contaminated with aflatoxins for evidence of mould, and discard any that look mouldy, discoloured, or shrivelled;
- avoid damage to grains before and during drying, and in storage, as damaged grain is more prone to invasion of moulds and therefore mycotoxin contamination;
- buy grains and nuts as fresh as possible;
- make sure that foods are stored properly – kept free of insects, dry, and not too warm;
- not keep foods for extended periods of time before being used; and
- ensure a diverse diet – this not only helps to reduce mycotoxins exposure, but also improves nutrition.

WHO response

WHO, in collaboration with FAO, is responsible for assessing the risks to humans of mycotoxins – through contamination in food – and for recommending adequate protection.

Risk assessments of mycotoxins in food done by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) are used by governments and by the Codex Alimentarius Commission (the intergovernmental standards-setting body for food) to establish maximum levels in food or provide other risk management advice to control or prevent contamination. Codex

standards are the international reference for national food supplies and for trade in food, so that people everywhere can be confident that the food they buy meets the agreed standards for safety and quality, no matter where it was produced.

JECFA set the tolerable intake level for many mycotoxins

JECFA or ad hoc FAO/WHO scientific expert groups consist of independent, international experts who conduct scientific reviews of all available studies and other relevant data on specific mycotoxins. The outcome of such health risk assessments can either be a maximum tolerable intake (exposure) level, or other guidance to indicate the level of health concern (such as the Margin of Exposure), including advice on risk management measures to prevent and control contamination, and on the analytical methods and monitoring and control activities.

These tolerable daily intakes are used by governments and international risk managers, such as the Codex Alimentarius Commission, to establish maximum levels for mycotoxins in food. The maximum levels for mycotoxins in food are very low due to their severe toxicity. For example, the maximum levels for aflatoxins set by the Codex in various nuts, grains, dried figs and milk are in the range of 0.5 to 15 μg/kg (a μg is one billionth of a kilogram). The Codex maximum limit for patulin in apple juice is 50 μg/L.

Exposure to mycotoxins needs to be kept as low as possible to protect the people. Mycotoxins not only pose a risk to both human and animal health, but also impact food security and nutrition by reducing people's access to healthy food. WHO encourages national authorities to monitor and ensure that levels of mycotoxins in foodstuff on their market are as low as possible and comply with the both national and international maximum levels, conditions and legislation.

4. Physical activity

KEY FACTS

- Physical activity has significant health benefits for hearts, bodies and minds
- Physical activity contributes to preventing and managing noncommunicable diseases such as cardiovascular diseases, cancer and diabetes
- Physical activity reduces symptoms of depression and anxiety
- Physical activity enhances thinking, learning, and judgment skills
- Physical activity ensures healthy growth and development in young people
- Physical activity improves overall well-being
- Globally, 1 in 4 adults do not meet the global recommended levels of physical activity
- People who are insufficiently active have a 20% to 30% increased risk of death compared to people who are sufficiently active
- More than 80% of the world's adolescent population is insufficiently physically active

What is physical activity?

WHO defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure. Physical activity refers to all movement including during leisure time, for transport to get to and from places, or as part of a person's work. Both moderate- and vigorous-intensity physical activity improve health.

Popular ways to be active include walking, cycling, wheeling, sports, active recreation and play, and can be done at any level of skill and for enjoyment by everybody.

Regular physical activity is proven to help prevent and manage noncommunicable diseases such as heart disease, stroke, diabetes and several cancers. It also helps prevent hypertension, maintain healthy body weight and can improve mental health, quality of life and well-being.

How much of physical activity is recommended?

WHO guidelines and recommendations provide details for different age groups and specific population groups on how much physical activity is needed for good health.

WHO recommends:

For children under 5 years of age

In a 24-hour day, infants (less than 1 year) should:

- be physically active several times a day in a variety of ways, particularly through interactive floor-based play; more is better. For those not yet mobile, this includes at least 30 minutes in prone position (tummy time) spread throughout the day while awake;
- not be restrained for more than 1 hour at a time (e.g., prams/strollers, high chairs, or strapped on a caregiver's back);
    - Screen time is not recommended.
- When sedentary, engaging in reading and storytelling with a caregiver is encouraged; and
- have 14-17h (0-3 months of age) or 12-16h (4-11 months of age) of good quality sleep, including naps.

In a 24-hour day, children 1-2 years of age should:

- spend at least 180 minutes in a variety of types of physical activities at any intensity, including moderate- to vigorous-intensity physical activity, spread throughout the day; more is better;

- not be restrained for more than 1 hour at a time (e.g., prams/strollers, high chairs, or strapped on a caregiver's back) or sit for extended periods of time.
  - For 1 year olds, sedentary screen time (such as watching TV or videos, playing computer games) is not recommended.
  - For those aged 2 years, sedentary screen time should be no more than 1 hour; less is better.
- When sedentary, engaging in reading and storytelling with a caregiver is encouraged; and
- have 11-14h of good quality sleep, including naps, with regular sleep and wake-up times.

In a 24-hour day, children 3-4 years of age should:

- spend at least 180 minutes in a variety of types of physical activities at any intensity, of which at least 60 minutes is moderate- to vigorous-intensity physical activity, spread throughout the day; more is better;
- not be restrained for more than 1 hour at a time (e.g., prams/strollers) or sit for extended periods of time.
  - Sedentary screen time should be no more than 1 hour; less is better.
- When sedentary, engaging in reading and storytelling with a caregiver is); encourage; and
- have 10-13h of good quality sleep, which may include a nap, with regular sleep and wake-up times.

For more information World Health Organization. Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age.

Children and adolescents aged 5-17 years

- should do at least an average of 60 minutes per day of moderate-to-vigorous intensity, mostly aerobic, physical activity, across the week.
- should incorporate vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, at least 3 days a week.
- should limit the amount of time spent being sedentary, particularly the amount of recreational screen time.

Adults aged 18–64 years

- should do at least 150–300 minutes of moderate-intensity aerobic physical activity;
- or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week
- should also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.
- may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits.
- should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits, and
- to help reduce the detrimental effects of high levels of sedentary behaviour on health, all adults and older adults should aim to do more than the recommended levels of moderate- to vigorous-intensity physical activity

Adults aged 65 years and above

- Same as for adults; and
- as part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity, on 3 or more days a week, to enhance functional capacity and to prevent falls.

Pregnant and postpartum women

All pregnant and postpartum women without contraindication should:

- do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week
- incorporate a variety of aerobic and muscle-strengthening activities
- should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits.

People living with chronic conditions (hypertension, type 2 diabetes, HIV and cancer survivors)

- should do at least 150–300 minutes of moderate-intensity aerobic physical activity;
- or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week
- should also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.
- as part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity, on 3 or more days a week, to enhance functional capacity and to prevent falls.

- may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits.
- should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits, and
- to help reduce the detrimental effects of high levels of sedentary behaviour on health, all adults and older adults should aim to do more than the recommended levels of moderate- to vigorous-intensity physical activity.

Children and adolescents living with disability
- should do at least an average of 60 minutes per day of moderate-to-vigorous intensity, mostly aerobic, physical activity, across the week.
- should incorporate vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, at least 3 days a week.
- should limit the amount of time spent being sedentary, particularly the amount of recreational screen time.

Adults living with disability
- should do at least 150–300 minutes of moderate-intensity aerobic physical activity;
- or at least 75–150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week
- should also do muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits.
- As part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity, on 3 or more days a week, to enhance functional capacity and to prevent falls.
- may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits.
- should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits, and
- to help reduce the detrimental effects of high levels of sedentary behaviour on health, all adults and older adults should aim to do more than the recommended levels of moderate- to vigorous-intensity physical activity.
- It is possible to avoid sedentary behaviour and be physically active while sitting or lying. E.g. Upper body led activities, inclusive and/or wheelchair-specific sport and activities.

Benefits and risks of physical activity and sedentary behavior

Regular physical activity, such as walking, cycling, wheeling, doing sports or active recreation, provides significant benefits for health. Some physical activity is better than doing none. By becoming more active throughout the day in relatively simple ways, people can easily achieve the recommended activity levels.

Physical inactivity is one of the leading risk factors for noncommunicable diseases mortality. People who are insufficiently active have a 20% to 30% increased risk of death compared to people who are sufficiently active.

Regular physical activity can:
- improve muscular and cardiorespiratory fitness;
- improve bone and functional health;
- reduce the risk of hypertension, coronary heart disease, stroke, diabetes, various types of cancer (including breast cancer and colon cancer), and depression;
- reduce the risk of falls as well as hip or vertebral fractures; and
- help maintain a healthy body weight.

In children and adolescents, physical activity improves:
- physical fitness (cardiorespiratory and muscular fitness)
- cardiometabolic health (blood pressure, dyslipidaemia, glucose, and insulin resistance)
- bone health
- cognitive outcomes (academic performance, executive function)
- mental health (reduced symptoms of depression)
- reduced adiposity

In adults and older adults, higher levels of physical activity improves:
- risk of all-cause mortality
- risk of cardiovascular disease mortality
- incident hypertension
- incident site-specific cancers (bladder, breast, colon, endometrial, oesophageal adenocarcinoma, gastric and renal cancers)

- incident type-2 diabetes
- prevents of falls
- mental health (reduced symptoms of anxiety and depression)
- cognitive health
- sleep
- measures of adiposity may also improve

For pregnant and post-partum women

Physical activity confers the following maternal and fetal health benefits: a decreased risk of:

- pre-eclampsia,
- gestational hypertension,
- gestational diabetes (for example 30% reduction in risk)
- excessive gestational weight gain,
- delivery complications
- postpartum depression
- newborn complications,
- and physical activity has no adverse effects on birthweight or increased risk of stillbirth.

Health risks of sedentary behaviour

Lives are becoming increasingly sedentary, through the use of motorized transport and the increased use of screens for work, education and recreation. Evidence shows higher amounts of sedentary behaviour are associated with the following poor health outcomes:

In children and adolescents:

- increased adiposity (weight gain)
- poorer cardiometabolic health, fitness, behavioural conduct/pro-social behaviour
- reduced sleep duration

In adults:

- all-cause mortality, cardiovascular disease mortality and cancer mortality
- incidence of cardiovascular disease, cancer and type-2 diabetes.

Levels of physical activity globally

- More than a quarter of the world's adult population (1.4 billion adults) are insufficiently active
- Worldwide, around 1 in 3 women and 1 in 4 men do not do enough physical activity to stay healthy.
- Levels of inactivity are twice as high in high-income countries compared to low-income countries,
- There has been no improvement in global levels of physical activity since 2001
- Insufficient activity increased by 5% (from 31.6% to 36.8%) in high-income countries between 2001 and 2016.

Increased levels of physical inactivity have negative impacts on health systems, the environment, economic development, community well-being and quality of life.

Globally, 28% of adults aged 18 and over were not active enough in 2016 (men 23% and women 32%). This means they do not meet the global recommendations of at least 150 minutes of moderate-intensity, or 75 minutes vigorous-intensity physical activity per week.

In high-income countries, 26% of men and 35% of women were insufficiently physically active, as compared to 12% of men and 24% of women in low-income countries. Low or decreasing physical activity levels often correspond with a high or rising gross national product.

The drop in physical activity is partly due to inaction during leisure time and sedentary behaviour on the job and at home. Likewise, an increase in the use of "passive" modes of transportation also contributes to insufficient physical activity.

Globally, 81% of adolescents aged 11-17 years were insufficiently physically active in 2016. Adolescent girls were less active than adolescent boys, with 85% vs. 78% not meeting WHO recommendations of at least 60 minutes of moderate to vigorous intensity physical activity per day.

How to increase physical activity?

Countries and communities must take action to provide everyone with more opportunities to be active, in order to increase physical activity. This requires a collective effort, both national and local, across different sectors and disciplines to implement policy and solutions appropriate to a country's cultural and social environment to promote, enable and encourage physical activity.

Policies to increase physical activity aim to ensure that:

- walking, cycling and other forms of active non-motorized forms of transport are accessible and safe for all;
- labour and workplace policies encourage active commuting and opportunities for being physically active during the work day;
- childcare, schools and higher education institutions provide supportive and safe spaces and facilities for all students to spend their free time actively;
- primary and secondary schools provide quality physical education that supports children to develop behaviour patterns that will keep them physically active throughout their lives;
- community-based and school-sport programmes provide appropriate opportunities for all ages and abilities;
- sports and recreation facilities provide opportunities for everyone to access and participate

in a variety of different sports, dance, exercise and active recreation; and
- health care providers advise and support patients to be regularly active.

WHO response

In 2018 WHO launched a new Global Action Plan on Physical Activity 2018-2030 which outlines four policy actions areas and 20 specific policy recommendations and actions for Member States, international partners and WHO, to increase physical activity worldwide. The global action plan calls for countries, cities and communities to adopt a 'whole-of-system' response involving all sectors and stakeholders taking action at global, regional and local levels to provide the safe and supportive environments and more opportunities to help people increase their levels of physical activity.

In 2018, the World Health Assembly agreed on a global target to reduce physical inactivity by 15% by 2030 and align with the Sustainable Development Goals. The commitments made by world leaders to develop ambitious national SDG responses provides an opportunity to refocus and renew efforts at promoting physical activity.

The WHO toolkit ACTIVE launched in 2019 provides more specific technical guidance on how to start and implement the 20 policy recommendations outlined in the global action plan.

The global action plan and ACTIVE propose policy options that can be adapted and tailored to local culture and contexts to help increase levels of physical activity globally, these include:
- the development and implementation of national guidelines for physical activity for all age groups;
- establishing national coordinating mechanisms involving all relevant government departments and key non-government stakeholders to develop and implement coherent and sustainable policy and actions plans;
- implementing community wide communication campaigns to raise awareness and knowledge of the multiple health, economic and social benefits of being physically active;
- invest in new technologies, innovation and research to develop cost effective approaches to increasing physical activity, particularly in low resource contexts;
- ensure regular surveillance and monitoring of physical activity and policy implementation.

To help countries and communities measure physical activity in adults, WHO has developed the Global Physical Activity Questionnaire (GPAQ). This questionnaire helps countries monitor insufficient physical activity as one of the main NCD risk factors. The GPAQ has been integrated into the WHO STEPwise approach, which is a surveillance system for the main NCD risk factors.

To assess physical activity among schoolchildren WHO has collaborated on a questionnaire module which has been integrated into the Global school-based student health survey (GSHS). The GSHS is a WHO/US CDC surveillance project designed to help countries measure and assess the behavioural risk factors and protective factors in 10 key areas among young people aged 13 to 17 years.

WHO is also working with international experts on the development of methods and instruments to assess physical activity in children under the age of five years of age and under 10 years of age. In addition, WHO is testing the use of digital and wearable technologies, such as pedometers and accelerometers, in national population surveillance of physical activity in adults. This work will be extended to include children and will inform the development of updated global guidance on the monitoring of physical activity and sedentary behaviours.

To support a 'whole of system' response, WHO is collaborating across multiple sectors to strengthen coordination, advocacy and alignment of policy and actions. WHO has established partnerships to help support Member States in their efforts to promote physical activity – these include working with the United Nations Educational, Scientific and Cultural Organization (UNESCO) to advance and align the implementation of GAPPA and the Kazan Action Plan on physical education, sports and physical activity. WHO is also working with many other UN agencies in the shared agenda to promote Sport for Development and Peace. Within the sports system WHO is collaborating with the International Olympic Committee and International Sports Federations, The International Federation of Football Associations, FIFA, and others to support and strengthen the promotion of health through sports and the sports for all agenda.

5. Schizophrenia

KEY FACTS
- Schizophrenia causes psychosis and is associated with considerable disability and may affect all areas of life including personal, family, social, educational, and occupational functioning.
- Stigma, discrimination, and violation of human rights of people with schizophrenia are common.
- More than two out of three people with psychosis in the world do not receive specialist mental health care.

- A range of effective care options for people with schizophrenia exist and at least one in three people with schizophrenia will be able to fully recover.

Symptoms

Schizophrenia is characterised by significant impairments in the way reality is perceived and changes in behaviour related to:

- persistent delusions: the person has fixed beliefs that something is true, despite evidence to the contrary;
- persistent hallucinations: the person may hear, smell, see, touch, or feel things that are not there;
- experiences of influence, control or passivity: the experience that one's feelings, impulses, actions, or thoughts are not generated by oneself, are being placed in one's mind or withdrawn from one's mind by others, or that one's thoughts are being broadcast to others;
- disorganized thinking, which is often observed as jumbled or irrelevant speech;
- highly disorganised behaviour e.g. the person does things that appear bizarre or purposeless, or the person has unpredictable or inappropriate emotional responses that interfere with their ability to organise their behaviour;
- "negative symptoms" such as very limited speech, restricted experience and expression of emotions, inability to experience interest or pleasure, and social withdrawal; and/or
- extreme agitation or slowing of movements, maintenance of unusual postures.

People with schizophrenia often also experience persistent difficulties with their cognitive or thinking skills, such as memory, attention, and problem-solving.

At least one third of people with schizophrenia experiences complete remission of symptoms (1). Some people with schizophrenia experience worsening and remission of symptoms periodically throughout their lives, others a gradual worsening of symptoms over time.

Magnitude and impact

Schizophrenia affects approximately 24 million people or 1 in 300 people (0.32%) worldwide. This rate is 1 in 222 people (0.45%) among adults (2). It is not as common as many other mental disorders. Onset is most often during late adolescence and the twenties, and onset tends to happen earlier among men than among women.

Schizophrenia is frequently associated with significant distress and impairment in personal, family, social, educational, occupational, and other important areas of life.

People with schizophrenia are 2 to 3 times more likely to die early than the general population (3). This is often due to physical illnesses, such as cardiovascular, metabolic, and infectious diseases.

People with schizophrenia often experience human rights violations both inside mental health institutions and in community settings. Stigma against people with this condition is intense and widespread, causing social exclusion, and impacting their relationships with others, including family and friends. This contributes to discrimination, which in turn can limit access to general health care, education, housing, and employment.

During humanitarian and public health emergencies, extreme stress and fear, breakdown of social supports, isolation and disruption of health-care services and supply of medication can occur. These changes can have an impact on the lives of people with schizophrenia, such as exacerbation of existing symptoms. During emergencies, people with schizophrenia are more vulnerable than others to various human rights violations, including neglect, abandonment, homelessness, abuse and exclusion.

Causes of schizophrenia

Research has not identified one single cause of schizophrenia. It is thought that an interaction between genes and a range of environmental factors may cause schizophrenia. Psychosocial factors may also affect the onset and course of schizophrenia. Heavy use of cannabis is associated with an elevated risk of the disorder.

Services

Currently, the vast majority of people with schizophrenia around the world are not receiving mental health care. Approximately 50% of people in mental hospitals have a schizophrenia diagnosis (4). Only 31.3% of people with psychosis receive specialist mental health care (5). Most resources for mental health services are inefficiently spent on care within mental hospitals.

There is clear evidence that mental hospitals are not effective in providing the care that people with mental health conditions need and, regularly, violate the basic human rights of persons with schizophrenia. Efforts to transfer care from mental health institutions to the community need to be expanded and accelerated. Such efforts start with the development of a range of quality community-based mental health services. Options for community-based mental health care include integration in primary health and general hospital care, community mental health centres, day centres, supported housing, and outreach services for home-based support. The engagement of the person with schizophrenia, family members and the wider community in providing support is important.

Management and support

A range of effective care options for people with schizophrenia exist, and these include medication, psychoeducation, family interventions, cognitive-behavioural therapy and psychosocial rehabilitation (e.g., life skills training). Facilitated assisted living, supported housing and supported employment are essential care options that should be available for people with schizophrenia. A recovery-oriented approach – giving people agency in treatment decisions – is essential for people with schizophrenia and for their families and/or caregivers as well.

WHO response

WHO's Comprehensive Mental Health Action Plan 2013-2030 highlights the steps required to provide appropriate services for people with mental disorders including schizophrenia. A key recommendation of the Action Plan is to shift services from institutions to the community. The WHO Special Initiative for Mental Health aims to further progress towards objectives of the Comprehensive Mental Health Action Plan 2013-2030 by ensuring 100 million more people have access to quality and affordable care for mental health conditions.

WHO's Mental Health Gap Action Programme (mhGAP) uses evidence-based technical guidance, tools and training packages to expand service in countries, especially in resource-poor settings. It focuses on a prioritized set of conditions, including psychosis, directing capacity building towards non-specialized health-care providers in an integrated approach that promotes mental health at all levels of care. Currently mhGAP is being implemented in more than 100 WHO Member States.

The WHO Quality Rights Project involves improving the quality of care and human rights conditions in mental health and social care facilities and to empower organizations to advocate for the health of people with mental health conditions and psychosocial disabilities.

The WHO guidance on community mental health services and person-centred and rights-based approaches provides information and support to all stakeholders who wish to develop or transform their mental health system and services to align with international human rights standards including the UN Convention on the Rights of Persons with Disabilities.

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