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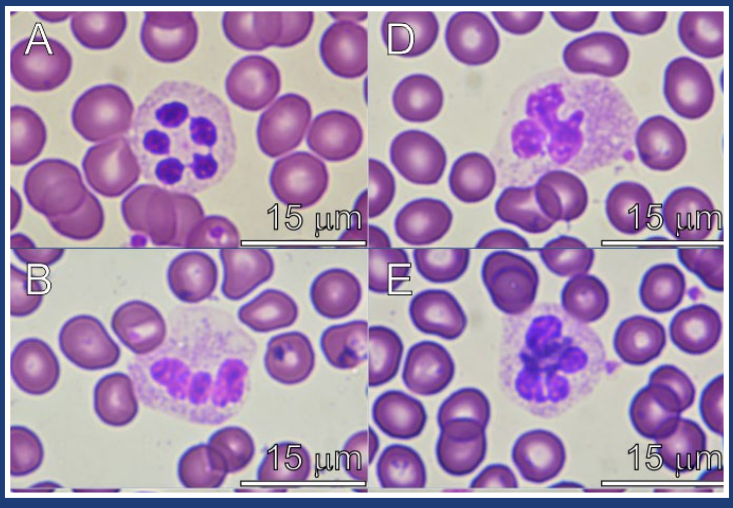

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Introduction

We are delighted to present the third issue of the "Medicine and Public Health Journal". This issue brings together six diverse articles that provide valuable perspectives on health, ethics and the ways in which humans adapt to medical and environmental challenges.

An original research article by Teleglow et al. delves into the fascinating world of winter swimmers, individuals who regularly immerse themselves in icy waters. The study examines how such extreme environmental exposure affects leukocyte apoptosis, shedding light on the adaptability and resilience of the human immune system.

This issue features two insightful review articles that address critical matters in public health and clinical practice. Prof Jan Hartman explores philosophical frameworks for redistribution of health care, contrasting entitlement-based approaches with solidarity-based models. Meanwhile, Stopyra' et al. highlight the complexity of diagnosing CMV infection. Using two illustrative case studies, the article highlights the broad spectrum of symptoms and the importance of a thorough differential diagnosis in infants with multi systemic presentations.

The case reports in this issue offer interesting perspectives on rare and challenging clinical scenarios. Milaniak et al. raise the issue of the cardiovascular risks of anorexia nervosa and the critical role of echocardiography in monitoring adolescent patients. Stachura et al. present the remarkable story of a pregnant patient undergoing awake neurosurgery, highlighting the importance of interdisciplinary care. Finally, Bogaczyk et al. explore the diagnosis of a congenital tumour identified postnatally, highlighting the value of neonatal screening and the complexity of managing such rare cases. Taken together, these case reports highlight the value of innovative and patient-centred approaches to the management of rare but important conditions.

We hope that you find the articles in this issue thought-provoking and informative, and that they stimulate both clinical and academic discussion. Thank you for joining us in exploring these diverse facets of medicine and public health. Enjoy reading!

Janusz Ligęza
Deputy Editor

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ORIGINAL RESEARCH PAPER

Leukocyte apoptosis in winter swimmers

Aneta Teleglow[1A,C-F], *Magdalena Kulpa*[B-D]

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: With regular cold baths, winter swimmers (individuals swimming in low-temperature water) develop an adaptation to the cold. Apoptosis is a fundamental process of the immune system; its main role consists in maintaining cell homeostasis to prevent the development of pathological conditions. The aim of this study is to investigate the effect of winter swimming on the apoptosis of peripheral blood leukocytes. It focuses on a unique and interesting aspect of winter swimming, providing vital insights into the immune system's physiological adaptations to harsh environments. The study investigates a relatively under-researched area, namely, the impact of winter swimming on leukocyte apoptosis, and thus makes a novel and relevant contribution to the fields of sports physiology and immunology, as understanding how regular exposure to cold water influences immune cell apoptosis can provide broader insights into the human body's adaptive mechanisms in the case of extreme environments.
Material and methods: The study group consisted of 9 male winter swimmers. After a bath, blood samples were collected from the ulnar vein. Blood smears were stained with the Hemacolor method. By light microscopy (1000×) under immersion, apoptotic forms were counted in the whole preparation relative to 100 leukocyte forms.
Results: Apoptotic leukocyte forms were very rare in the participants' blood. Out of the 9 subjects, only 3 individuals exhibited 2%–3% of leukocyte apoptotic forms.
Conclusions: The findings demonstrate that low water temperature does not cause significant leukocyte apoptosis in winter swimmers, which is an important finding. This suggests that regular exposure to cold water may improve immunological resilience, which is a favourable adaptation for those who participate in this sport.
Keywords: winter swimming, blood, apoptosis

Introduction

Winter swimmers regularly bathe in ice holes, lakes, rivers, and seas during winter. They have implemented this type of alternative medicine, treating it as a hobby. This extreme sport positively affects the lives of winter swimmers by toughening their bodies. Cold water immersion is associated with physiological changes in the respiratory, circulatory, and endocrine systems, and also influences the morphological and rheological properties

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of the blood [1]. The human body is characterized by homeothermy, which denotes keeping a constant body temperature under various conditions and promotes maintaining homeostasis in the body. Extreme body cooling under aquatic conditions can lead to hypothermia; the human body defends itself against this by activating such mechanisms as constriction of cutaneous blood vessels and increased metabolic heat production by exertion or muscle shivering [1,2]. With regular cold baths, winter swimmers develop adaptation to the cold, which translates into resistance to respiratory infections, reduced cardiac output and heart rate, as well as increased vasoconstriction within the skin [3].

The aim of this study was to investigate the effect of winter swimming on the apoptosis of peripheral blood leukocytes in winter swimmers.

Material and methods

The study group consisted of 9 male winter swimmers swimming in low-temperature water (2–7.2°C) during the winter season, lasting from November to March. The participants were affiliated to the Krakow Society of Winter Swimmers "Kaloryfer" in Krakow (Poland). After a bath, a qualified nurse collected blood samples from the ulnar vein of each winter swimmer into Vacuette tubes, after which they were transported to the Blood Physiology Laboratory of the Central Research and Development Laboratory, University of Physical Education in Krakow. A limitation of the study is that only a small number of winter swimmers took part.

The study was approved by the Ethics Committee of the Regional Medical Chamber in Krakow and carried out in accordance with the principles of the Declaration of Helsinki. All subjects provided their informed consent to participate in the study.

Cytological examination

2 ml of blood was collected from each participant in accordance with the current standards. In the Blood Physiology Laboratory of the of the Central Research and Development Laboratory, University of Physical Education in Krakow, smears were performed on a basic slide. The smears were allowed to dry for 12 hours to prefix the cells on a basic slide. After 12 hours, the blood smears were stained using the Hemacolor method (a modification of the May-Grünwald-Giemsa method), Merck catalog No. 107961. The preparation was washed with a buffer solution of pH 6–8. Then, by light microscopy (1000×) under immersion, apoptotic forms were counted in the whole preparation relative to 100 leukocyte forms encountered in the blood smear. The results were reported in percentages.

Results

Out of the 9 subjects, 3 individuals exhibited 2–3% of leukocyte apoptotic forms. These are illustrated in Figure 1.

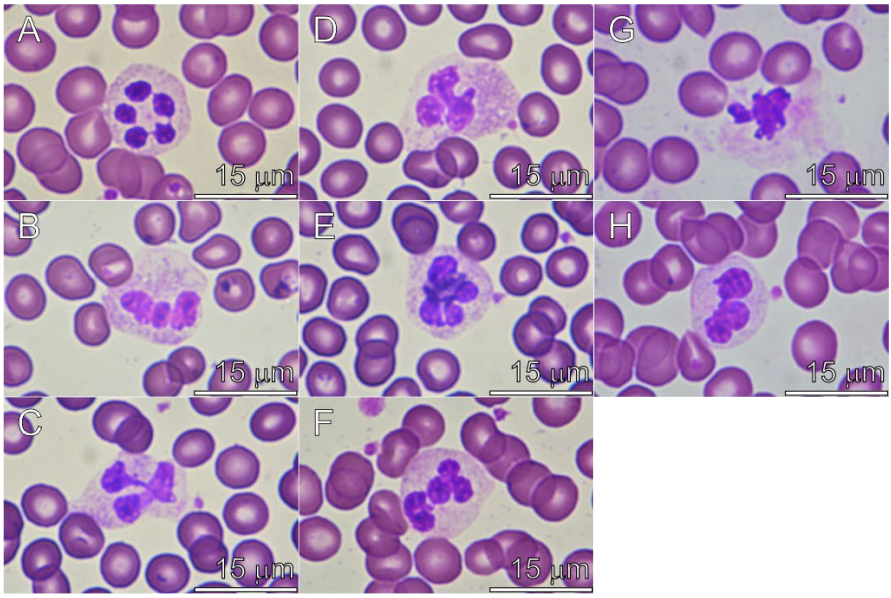

Figure 1 (A) A neutrophilic granulocyte. Clustered lobes of the cell nucleus, partially degenerating. Developing apoptosis. (B) A neutrophilic granulocyte. The lobes of the nucleus close together, invisible "bridges" between the nucleus lobes. Early stage of apoptosis. (C) An eosinophil with a degenerating nucleus. Pre-apoptotic form. (D) A neutrophilic granulocyte with a degenerating nucleus. Pre-apoptotic form. (E) A neutrophilic granulocyte. Aging form, nonapoptotic. (F) A neutrophilic granulocyte. Early apoptosis. (G) A neutrophilic granulocyte. Loss of granulation, complete apoptosis: cell disintegration. (H) A neutrophilic granulocyte. Early apoptosis

Discussion

The aim of this study was to investigate the effect of winter swimming on peripheral blood leukocyte apoptosis in individuals swimming in cold waters. Previously, no study had been conducted with this purpose. Apoptosis plays an important role in the human body; it is a fundamental process of the immune system [4]. Between 5,000 and 8,000 leukocytes, or white blood cells, are formed in the red bone marrow. Taking into account the proportion and type of granules in the cytoplasm, leukocytes can be divided into granulocytes (granular) and agranulocytes (nongranular). Granulocytes are characterized by a segmented nucleus and apparent granules. They can

be neutrophilic (neutrophils), acidophilic (eosinophils), or basophilic (basophils). Agranulocytes do not exhibit granularity, and their nucleus is rounded or kidney-shaped. Among agranulocytes, one distinguishes monocytes and lymphocytes [5,6]. Neutrophils – neutrophilic granulocytes – are about 12 μm in size, with a segmented nucleus depending on the cell maturity; the "younger" they are, the fewer lobes they have. They possess granules of two types: primary (nonspecific) and secondary (specific). They contain lysozyme, defensins, cathepsins, and myeloperoxidase. They are responsible for the first line of defence against microbial infection; their presence indicates acute inflammation. The defensive activities of neutrophils include microorganism phagocytosis, microorganism killing, and the ability to move (chemotaxis). Their lifespan ranges from several hours in the blood to about 2–3 days after migrating to tissues. Eosinophils – acidophilic granulocytes – account for 40% of all leukocytes. They have a diameter of 14 μm and are distinguished by an "ocular" nucleus. Eosinophil granules involve major basic proteins, eosinophil cationic protein, and eosinophil-derived neurotoxins. The function of eosinophils is to kill multicellular organisms and neutralize inflammatory mediators [5–7]. Basophils – basophilic granulocytes – make up only 1% of leukocytes. They are 12 μm in size, are associated with the development of allergic reactions, and possess receptors for IgE antibodies. Their primary function is to prevent blood clotting [5,6]. Lymphocytes – nongranular leukocytes – constitute the smallest blood component (8 μm). In turn, monocytes, with a diameter of 20 μm, are considered to be the largest morphological elements of blood. Their nucleus is kidney-shaped. They remain in blood for 1–2 days, have phagocytosis capacity, and are involved in the production of immunity-related factors. They also transform into large phagocytic cells capable of absorbing and digesting bacteria or the remains of damaged cells [5–7].

Programmed cell death (i.e., apoptosis, a term introduced in 1972 by Kerr et al.) is a physiological, active mechanism that determines the proper functioning of the organism. The process of apoptosis creates a pattern of eliminating superfluous cells or tissues in the body, which allows the normal number and quality of cells to be maintained [8,9]. Cells that degenerate in the course of apoptosis present characteristic morphological and biochemical changes. The loss of intracellular water and electrolytes in a single cell results in the cell shrinking, as well as in changes in shape, size, and cytoplasm density. The cell surface becomes corrugated; chromatin condensation occurs and nuclear DNA is fragmented [10,11]. Apoptotic bodies are formed, which are surrounded by cytoplasmic membrane and contain a DNA fragment and "healthy" organelles [11]. They are subsequently phagocytosed by macrophages and the surrounding cells. No inflammatory

process develops, as the cell membrane does not lose its continuity or function, which is of crucial importance [8].

There are two main apoptosis pathways: extrinsic (receptor-mediated) and intrinsic (mitochondrial). Both activate the caspase cascade, which is responsible for triggering the process. Caspases are cysteine protease enzymes that destroy enzymatic and structural proteins, which leads to complete cell disintegration [4,11].

Intrinsic apoptosis is initiated by heat shock, oxidative stress, or DNA damage. The mitochondrial membrane loses its continuity, forming a mitochondrial permeability transition pore, through which cytochrome c enters the cytoplasm. Cytochrome c then combines with Apaf-1 proteins and procaspase-9 to form a complex called the apoptosome. The apoptosome stimulates caspase-9, which subsequently activates the executive caspase – caspase-3. Flavoprotein, which constitutes an apoptosis-inducing factor, and endonuclease G enter the cell nucleus, contributing to DNA fragmentation and nuclear chromatin condensation [12–15].

Extrinsic apoptosis occurs by the activation of the death receptor in the cell membrane. Death receptors include proteins involving tumour necrosis factor (TNF), e.g. TNFR1, TNFR2, Fas/CD95/Apo-1, or TRAIL/Apo2. The interaction between membrane receptors and ligands leads to changes in the structure of intracytoplasmic domains, so-called death domains. The death signal then travels to the adaptor protein of the Fas-associated death domain protein [8,10,15,16].

In the erythropoietic system, Cowling and Dexter [17] demonstrated erythropoietin, the stem cell factor, and insulin-like growth factor 1, reducing the apoptotic death of erythroid progenitor cells. They indicated that a deficiency of these growth factors stopped heme synthesis, which contributed to progenitor cell death.

Factors that inhibit the process of apoptosis also include the hematopoietic growth factor in granulocyte-macrophage progenitor cells. More precisely, the granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), and interleukin 3 (IL-3) have an impact on both the development and death in the granulocyte-monocyte hematopoietic lineage [18,19].

Vermes and Haanen [20] confirmed that GM-CSF, G-CSF and IL-3 regulated the development and differentiation of neutrophils, increasing their survival, and simultaneously suppressed apoptotic death. Biffl et al. [21] also demonstrated that IL-3 delayed neutrophil apoptosis. However, eosinophil death was decreased by IL-5.

The results of studies conducted in normal and leukemic myeloid cell

populations demonstrate the occurrence of apoptotic death in the absence of growth factors or modifications at the level of apoptosis resulting from interactions among the cytokines on which these cells depend in terms of survival [6,18,22,23].

Studies have been performed in the immune system concerning the effects of cytokines on myeloid-derived B cells, thymus-derived T cells, and natural killer (NK) cells. Koury [18] observed mature T cells undergoing apoptosis in the absence of either IL-3 or IL-6. Haanen and Vermes [24] detected IL-2-dependent T lymphocytes that had undergone apoptotic death after being deprived of access to this cytokine. In turn, Lømo et al. [25] demonstrated that transforming growth factor β induced apoptosis in resting peripheral blood lymphocytes *in vitro*, and IL-4 partially inhibited apoptotic death caused by transforming growth factor β.

The impact of cytokines on the above-mentioned cells has been observed in *in vitro* studies, which allow the examination of several arbitrary cytokines. Both inhibition and increase of programmed cell death are of significance in the immune system [19,26].

Apoptosis is induced by biological factors (TNF, glucocorticoids, growth factor deficiency), physical factors (ionizing radiation, temperature shock), or chemical factors (cytostatics, oxidative stress caused by oxygen free radicals) [8,9]. Seki et al. [27] investigated the effect of γ-radiation on the level of apoptotic death in lymphocyte subpopulations. NK cells proved to be the most radioresistant to apoptosis, T lymphocytes $CD8^+$ and B lymphocytes exhibited poor sensitivity, while T lymphocytes $CD4^+$ turned out to be relatively resistant to apoptotic death. Delic et al. [28] also observed apoptotic death in human lymphocytes after fractional γ-ray irradiation *in vivo*. Grelli et al. [29] identified apoptotic death of lymphocytes induced by prostaglandin E2 $9PGE_2$. Another physical factor increasing apoptotic death is hyperthermia, which affects the bone marrow, thymus, spleen, and lymph nodes [30]. Natural cell suicide is inherent in the proper function of the immune system. During leukocyte maturation in the thymus, cell selection occurs to prevent intolerance of own antigens [4]. Increased apoptosis contributes to the development of degenerative diseases, such as Alzheimer's disease or Parkinson's disease, or infectious diseases, e.g. AIDS or hepatitis [9,11]. In turn, a decrease in this process leads to the onset of malignancies, autoimmune diseases, or viral infections [8]. Cytokine proteins exert a large impact on immune system cells. Their role in this system consists in regulating cell growth and maturation, as well as in controlling cell death. The influence of cytokine on immune system cells, the populations of myeloid-derived B cells, thymus-derived T cells, and NK cells is complex [19,31].

This study, however, revealed that apoptotic leukocyte forms were very rare in the participants' blood: they were only detected in 3 winter swimmers. Methods for detecting apoptosis are constantly being modified, as understanding the relationships between molecules involved in its regulation contributes to improvements in diagnosis.

Conclusions

The findings demonstrate that low water temperature does not cause significant leukocyte apoptosis in winter swimmers, which is an important finding. This suggests that regular exposure to cold water may improve immunological resilience, which is a favourable adaptation for those who participate in this sport.

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REVIEW PAPER

Rights or solidarity? In search of international justice in healthcare

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: There are two models for legitimizing the redistribution: an entitlement-based model and one based on solidarity. In both cases we are dealing with moral obligation; however, not imperative. In the legal model, one often refers to s.c. imperfect duty, while in the solidarity model we are dealing with a moral duty based on values. I defend the idea of justifying redistribution by referring to the principle of solidarity combined with the idea of sustainable development.
Material and methods: This a philosophical paper in healthcare ethic.
Results: The result of the discussion is my proposal to combine categories of sustainable development and solidarity to provide justofication for the global redistribution of healtcare resources.
Conclusions: Solidarity is a pragmatic and proactive relationship, flexible and open to the various beliefs and motivations of the cooperating parties. Therefore, the language of solidarity is more universal and promising in the work of building a global health system in which developing countries can feel safe and treated fairly, rather than a language that speaks of entitlements, obligations and charity. Building a climate of trust and pursuing socially responsible sustainable development policies do not require strong theories of justice or other rigid legal or ethical doctrines. Such doctrines can even be harmful. Meanwhile, the discourse relating to solidarity, trust-building and cooperation to achieve realistic and reasonable goals at the transnational public health level is relatively undoctrinaire, and instead flexible and open to a variety of interpretations. In the realities of international politics and cooperation, these are serious advantages.
Keywords: justice, healthcare, redistribution, solidarity

Introduction

The purpose of this article is to contribute to the debate regarding the principle of legitimizing the provision of healthcare resources to poorer countries by wealthier countries. There are two basic models for legitimizing the redistribution of healthcare resources: an entitlement-based model (human rights and the right to minimum health care) and one based on solidarity. In both cases we are dealing with moral obligation, although not a moral

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imperative. In the legal model, one often refers to so-called imperfect duty, while in the solidarity model we are dealing with a moral duty based on the virtues and values of those called to action. In this article, I will defend the idea of justifying redistribution by referring to the principle of solidarity combined with the idea of sustainable development. Solidarity is an ethical ideal that presupposes joint activity, i.e. cooperation, while the right to receive support is realized indirectly and in effect ceded to public institutions. Sustainability is an imperative dictated by prudence. Both solidarity and sustainability are categories that go beyond the opposition of selfish and altruistic action.

Beyond the charity model

In the field of public health ethics, the issue of equitable redistribution of public funds for health services – both nationally and globally – is crucial. One of the widely debated issues is the nature and scale of the obligations of rich Western countries to developing countries. In this context, the question arises as to the legal and ethical basis for the diversion of funds from national budgets for the medical purposes of the populations of less developed countries and regions of the world. This question is crucial in this regard. When richer countries have an interest in supporting the countries of the global South, then it is right that this interest justifies engaging in redistribution. However, if the benefits cannot, even in the long term, be pointed out, another justification is necessary. Probably most of us feel that supporting the poorer is right and even morally necessary, but we differ on how it should be understood and what principles of redistribution should be adopted when they are not defined in terms of entitlements, as is the case for the insured citizens of a country where public health budget exists.

With regard to areas such as infectious disease prevention, the interest is mutual: investing resources in preventing epidemics in Africa or Asia simultaneously protects Western societies. The case is different, however, with financial transfers whose sole, or in any case overriding, purpose is simply to help those in need in developing countries. These are transfers that are wholly or partially (i.e. in some areas) altruistic and therefore inexplicable in the narrow perspective of rational management of national resources and the logic of costs and effects. In order for them to be serious and sustainable, public health doctrines and, consequently, the laws of rich Western countries must use moral justification, based on plausible moral ideas rather than emotions. The concept of sustainable development, based on social responsibility and principally opposed to great social inequalities, either local or global, appeals to the notion of justice and to prudence, obliging us to

avoid risky and uncontrollable situations; these include serious deficits and inequalities in access to critical goods, including health benefits. Sustainable development, based on a balance of environmental, social and economic factors, is in the common interest of all humanity, and the related policies are something to which their beneficiaries are entitled, both in local and global systems of social justice. Thus, it is possible to speak of a universal human solidarity reinforced by a shared global fate and global threats. This means that the practice of solidarity is the basis of sustainable development. Still, the driving force behind solidarity-based practices is the time-honoured and essentially conservative idea of the duty to help one's neighbour in need. There is a certain dissonance and inconsistency here, stemming from the popular conviction that the motivation for action can be either self-interest or the ideal of selfless, altruistic doing good. Perhaps one should go beyond this opposition, bearing in mind that actions can have mixed motivation and not at all be based on separating one's own benefit (for example, the national benefit) from that of another (for example, another nation).

The very phrase 'providing help' – so strongly associated with an attitude of altruism – can be controversial, as activity referred to in this way (or similarly, for example, referred to as 'support') is regarded as entirely voluntary and always praiseworthy, reducing relations with recipients of 'help' to the level of donors and beneficiaries of charity. As a result of discussions concerning the concepts of classical liberalism and libertarianism, the social and political consensus has long been established that reducing international aid to the category of charity is wrong and harmful, not least because it deprives the beneficiaries of all rights to criticize and express dissatisfaction with the scope and form of the aid they receive. This does not mean that charity is wrong in itself, but only that, as the dominant pattern of providing support, it has a condescending quality to it and perpetuates inequality, placing the beneficiaries in a subordinate position and even in the position of never grateful enough and insolvent debtors. In addition, charity is always more or less fragmentary and offers no guarantee of continuity or lasting security for the beneficiaries' needs. Therefore, the social policies of Western countries, especially so-called welfare states, are looking for a more secure doctrinal basis for themselves, in the sense of both legal and ethical doctrine. The matter is not settled, however. We are still not sure whether the category of charity and activities subordinated to the logic of charity in principle and over the long term serve the good of the needy, or whether they limit the development of the real entitlements of economically weaker individuals and communities, leaving too much in the field of public policies to the whims of goodwill. In order to answer these questions and formulate an international consensus on the doctrinal foundations of financial and technological

transfers from rich countries to developing countries, it is necessary to adopt some resolution on how collective and institutional obligations are born and what the limits of the obligation to take care of other people's welfare are, i.e., according to what criteria its scope should be determined. The simplest and most popular answer to these questions appeals to the notion of solidarity (one should bring help, because this is what natural solidarity with the weaker requires) and the notion of satisfying minimum needs (by drawing a line between minimal and supra-maximal actions, we make it possible for a greater number of those in need to benefit from the always limited resources and ensure that they are used sparingly).

Hassoun vs. Hausman

An expression of how lively the discussion is regarding these issues is Daniel Hausman's very interesting polemic [1] with Nicole Hassoun, the author of the book *Global Health Impact: Extending Access to Essential Medicines* [2], featured in the special issue of Developing World Bioethics published on 22.06.2022. In her book, Hassoun defends the model of global redistribution in health care based on the obligation to ensure a minimum quality of life for all people. The basis of redistribution is thus a universal entitlement to minimal medical care. Hausman, on the other hand, points out the paradoxes inherent in this position, while referring to the ethical concept of imperfect duties, which derives from the work of Immanuel Kant and is rooted in the traditions of Roman law (*lex imperfecta*). Ultimately, Hausman defends the position that the global redistribution of healthcare resources belongs precisely to imperfect duties, that is, duties that can be fulfilled indirectly, but through others – for example, dedicated state institutions – with no sanctions for failure to fulfill such duties [3]. I think a compromise between both positions is possible.

Hausman is right when he points to the statistical dimension of medical needs. Disease prevention, such as vaccination against COVID-19, has such a huge impact on the well-being of society that one can speak of an elementary interest that society has in taking advantage of available means of preventing diseases that cause a statistically large number of deaths. However, if the threat of death from an unfavourable epidemiological situation, for example, from an infectious disease epidemic, means a risk of death for one in a thousand, it can hardly be said that the use of a preventive procedure (e.g., vaccination) in this case is the safeguarding of a person's minimum health needs. If the right to minimum health care is a human right, and therefore an individual right, then it would not be easy to justify international aid for disease prevention in a given country using this category. It appears, however,

that the source of moral obligation in this case is the collective, not individuals taken in isolation, just as the responsibility for providing assistance rests with the collective and its institutions, not with individuals.

Nicole Hassoun derives the right to minimal medical care from the more general right to a minimally good life. Unfortunately, as Daniel Hausman points out, quality of life is largely left to the subjective judgment of each individual. Many people who are seriously ill and deprived of medical care for various reasons may think they have a good life and even consider themselves happy. Nevertheless, in the vast majority of cases, a serious and painful illness makes a person unhappy, and it is reasonable to accept as a rough generalization that this or that illness excludes a minimally good life in many cases. It does not follow from the fact that a certain number of people with serious parasitic diseases are happy that we do not have a moral obligation to share with developing countries the medical means to treat them. And arguably, we also have this obligation in the case of those parasitic diseases that are so chronic that they are rarely the main cause of the patient's death. On the other hand, Hausman's observation that what we might define as minimal medical care in many cases constitutes less than we would like to provide for the people whose fate we really care about also seems correct. So there is a certain harshness in 'redistributive minimalism' that does not correspond to the fundamental intention behind acts of solidarity, including international solidarity. Minimalism in providing aid has its rationale in increasing the number of beneficiaries while maintaining the same pool of resources, which is always insufficient to meet all needs. At the same time, however, minimalism reveals a fundamental reluctance to engage in aid, which appears as a kind of 'necessary evil.' However, is helping really something we should avoid and always fulfill only minimally? Probably not – the rationale for helping is generosity rather than stinginess, as well as a sense of solidarity rather than a moral imperative to save, capable of affecting us strongly enough to overcome our selfishness.

Towards solidarity

In their programmatic article *The Place of Solidarity in Public Health Ethics* [4], Angus Dawson and Bruce Jennings advocate overcoming traditional liberal individualism in public health ethics and taking as a starting point a vision of the individual as a being in all aspects of his or her life, practices and socialized activity. The expression of this change of point of view in public health ethics should be to give an entirely new prominence to the hitherto undervalued category of solidarity. In the concept of solidarity they present, the metaphor of 'standing by' plays a key role. This concept can be

understood in a variety of ways, but the authors are concerned with the creation of a natural community of action in the face of an emerging problem and the resulting task to deal with it. As they write, 'If I am healthy and you are sick, the appropriate response is not one merely of pity or even sympathy by me toward you, but rather seeing that there is a connection between us' [4:77].

I agree with this position. Solidarity is not based on interest or calculation or emotion but is in itself a proactive attitude in which other people's problems are recognized with one's own simply because other people are important and matter. A goal-oriented and straightforward or direct attitude towards another whose difficulties and needs become a challenge and a call to action is meant to replace a deliberative attitude towards a stranger who, on the basis of some justification, should be included in some system of mutual concern and justice. The concept of solidarity as a basis for action for the good of those who cannot reciprocate the benefits received treats the attitude of solidarity as a self-evident good that does not require justification. Such a justification could be the religious idea of mercy, the idea of brotherhood, or the idea of a shared human condition Each of these, like the appeal to emotion and the capacity for empathy, is particularistic in nature and thus unsuitable for universal application as the basis of a global system of benefit distribution.

Peter G.N. West-Oram and Alena Buyx [5:213] define solidarity as an "enacted commitment to carry 'costs' (financial, social, emotional, or otherwise) to assist others with whom a person or persons recognize similarity in a relevant respect," emphasizing that recognition of similarity is different from empathy. Like most authors who write about solidarity, they link it to the community based on the similarity that all people share. We act together for common goals and support each other because we are alike – this is how the argument for solidarity as a driver of global public health can be summarized. West-Oram and Buyx realize the inverse relationship between the cohesive force of solidarity and the size of the group within which solidarity is supposed to motivate action. At the pan-human level, this force is still small. It may, however, gradually increase. However, what makes the category of solidarity remain useful in spite of everything is the local and 'projective' nature of any action resulting from a sense and attitude of solidarity. For our actions are never (except perhaps at the UN or WHO level [6]) addressed to all people, but to some group that becomes close to us precisely because we begin to engage with these people and serve their welfare.

Redistribution of healthcare resources internationally cannot be based solely on goodwill or arbitrarily granted entitlements. The obligations of rich countries to countries and regions in need of support should not be

arbitrary and adopted unilaterally. If we are to take redistribution seriously, all stakeholders must be treated in just such a serious and respectful manner. If the basis for cooperation is solidarity and social responsibility within the framework of a global policy of sustainable development, those responsible for health care in the donor country and in the beneficiary country must treat each other as partners, working together with the single goal of improving the health of a particular community. The direction of the flow of funds is only one of the considerations that must be taken into account here. Under conditions of solidarity, joint action is triggered not by an interest, but by a need and an appeal for help in solving a problem.

Of course, solidarity is grounded in certain real links between the interacting parties, in commitments made, as well as in interests and benefits. In an international system of cooperation based on the shared ideals of sustainability and solidarity, there is no need to maintain a separation between action based on interest and altruistic action. Nor is there a need to value them. Evaluating the attitudes of cooperating parties does not have to presuppose a calculation of proportions between what is driven by interest, by a propensity for charity or by respect for rights to minimum health care.

Conclusion

Solidarity is a pragmatic and proactive relationship, flexible and open to the various beliefs and motivations of the cooperating parties. Therefore, the language of solidarity is more universal and promising in the work of building a global health system in which developing countries can feel safe and treated fairly, rather than a language that speaks of entitlements, obligations and charity. Building a climate of trust and pursuing socially responsible sustainable development policies do not require strong theories of justice or other rigid legal or ethical doctrines. Such doctrines can even be harmful. Yet we know in advance that not all cooperating parties will be able to share these doctrines. Meanwhile, the discourse relating to solidarity, trust-building and cooperation to achieve realistic and reasonable goals at the transnational public health level is relatively undoctrinaire, and instead flexible and open to a variety of interpretations. In the realities of international politics and cooperation, these are serious advantages.

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CASE REPORT

Cytomegalovirus infection – the need for detailed differential diagnostics

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: Cytomegalovirus infection represents the most common congenital and acquired infection. The symptomatology is very broad and usually non-specific, ranging from asymptomatic forms to status with organ damage or even to severe systemic infection. This makes CMV infection mimic other disorders and diseases.
Case description: Here we report two cases of CMV infection diagnosed after the second month of life in children who were referred to the infectious disease ward for extended diagnosis. Despite the late identification of infection, the clinical manifestation (psychomotor retardation, hearing loss, lenticulostriate vasculopathy) suggested a diagnosis of congenital infection was highly probable.
Discussion and evaluation: The further diagnostic process led to the correct diagnoses of congenital heart defect and cystic fibrosis, and administration of adequate specialist treatment.
Conclusions: CMV infections are common and it is worthy to remember that the diagnosis of CMV infection can be not the only one in multisymptomatic infants so the thorough differential diagnostics is necessary.
Keywords: cystic fibrosis, congenital infection, psychomotor retardation, cytomegalovirus infection, heart defect

Introduction

Even though cytomegalovirus infection is common in the population, diagnostic and therapeutic challenges are still encountered in clinical practice; this is particularly true in the case of congenital CMV infection. The symptoms of CMV infection may also be the same for other diseases, and since it is common in infants, its identification should not prompt one to abandon the process of full differential diagnosis. The cases reported below

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concern confirmed CMV infections that had probably been acquired and had an asymptomatic course, whereby the observed signs and symptoms, although coincidentally similar to those appearing in congenital infections, resulted from other serious conditions.

Case 1

A 6-month-old girl, diagnosed with psychomotor retardation, was referred to our department following a diagnosis of CMV infection. The child was a full term-neonate, of the second pregnancy and second birth, with a birth weight of 3520 g and 10 points on the Apgar scale. The first (screening) hearing test was normal. Psychomotor retardation was observed from the second month of life. Physical examination revealed dysmorphic features (flat occiput, wide-set eyes, low-set ears, short neck). Moreover, generalized hypotonia was observed. A consultation with a neurologist took place, and intensive rehabilitation was initiated. An outpatient transfontanelle US scan revealed lenticulostriate vasculopathy. The diagnosis was extended to include serology tests which showed positive IgM and IgG anti-CMV antibodies. The girl was referred to the hospital (at the age of six months) with a suspicion of congenital cytomegalovirus infection. In our department additional test results were as follows: urine CMV PCR – positive; blood CMV PCR 1000 copies/ml; CSF CMV PCR – negative. It was not possible to perform a CMV PCR test on the dried blood spot collected from the newborn screening test. The ABR test showed profound hearing impairment. Because of the child's age at the diagnosis, it was impossible to determine whether the infection was congenital or acquired, but the signs (lenticulostriate vasculopathy, hearing loss and psychomotor retardation) and confirmed positive CMV PCR tests made a diagnosis of congenital infection highly probable. On admission to our department both high-frequency, loud, grade IV/VI systolic murmur along the left sternal border and tachycardia were found. The circulatory insufficiency was diagnosed and the treatment started. Cardiac ECHO demonstrated a transitional atrioventricular septal defect. Soon some improvement was seen in the child's psychomotor development. At 13 months, the congenital heart defect was repaired, and within 3 months after the cardiac surgery, the child's psychomotor development improved significantly. The girl started to walk at the age of 21 months, and a follow-up ABR examination revealed normal hearing. Due to subtle dysmorphic features, the child was referred to the Genetics Clinic; the test results returned normal.

Case 2

A 2.5-month-old boy was admitted to our so that diagnosis of a cytomegalovirus infection could be continued and treatment begun. The child was born at 39 weeks of gestation (para 1, gravida 1, natural delivery) with a birth weight of 3300 g and Apgar score of 10. The maternal obstetric interview disclosed controlled gestational diabetes (dietary management), Hashimoto's thyroiditis (euthyroid), a normal TORCH screen and tests for other infectious agents; the mother was not tested for a CMV infection. The results of neonatal screening and hearing tests were normal. Due to poor weight gain (about 300 g per month; the boy was fed with expressed breast milk) and persisting diarrhoeal stools (watery, celadon in colour), an outpatient CBC was ordered which revealed significant anaemia (Hb 8.5 g/dl). The child was initially referred to the district hospital where packed red blood cells were transfused, and then the boy was transferred to a university hospital. Upon admission to the clinical ward, the physical examination revealed pale skin with numerous, fine papular lesions with signs of superinfection and a haemorrhagic component at the elbow flexor surfaces, inner thighs, chin and neck, and pitting oedema, mainly of the lower legs. The laboratory findings were as follows: evident improvement of red blood cell parameters (Hb 10.9 g/dl, Hct 32.2%), thrombocytopenia (118 000/µl), hypoproteinaemia (24.5 g/l), hypoalbuminaemia (11.5 g/l), elevated transaminases ALT 71 U/l, AST 107 U/l (RR ALT 0–55 U/l, AST 5–34 U/l) signs of cholestasis GGT 152 U/l (RR 12–64 U/l), coagulation disorders (prolonged PT, hypofibrinogenaemia), and signs of subclinical hypothyroidism. Stool analysis revealed occult blood, while serology was positive for IgM and IgG antibodies against CMV and Parvovirus B19. CMV DNA was found in the urine (by PCR). It was not possible to test for CMV PCR on the dried blood spot from the screening sample taken at birth. An abdominal US scan revealed a thickened, hypoechoic gallbladder wall. An elemental formula was administered for feeding with a good result. The child was transferred to our department for extended diagnosis and possible treatment of the CMV infection. In our department, vertical and active infections with Toxoplasma gondii, HCV, HSV and HIV was excluded. In an ophthalmologic examination no irregularities were found. The alpha-1 antitrypsin and ceruloplasmin concentrations were normal. The patient was still fed with an amino acid formula, and vitamin supplementation was begun with good tolerance and with weight gain. The entire clinical picture indicated a cytomegalovirus infection with concomitant enteritis. Furthermore, a sweat test was performed as part of the diagnostic workup and revealed a high sweat chloride level 110 mmol/L (RR 20–40 mmol/L). The boy was immediately referred to

a cystic fibrosis clinic. Finally, genetic tests confirmed a classic (typical) form of cystic fibrosis.

Discussion

Cytomegalovirus is a species-specific virus and is one of the eight human herpesviruses (HHV5); taxonomically, it belongs to the family *Herpesviridae* and the subfamily *Betaherpesvirinae*. It is characterized by a long incubation period (4–8 weeks), long replication (24–72 hours) and may also be a significant factor in the reactivation of other herpesviruses. The worldwide prevalence of CMV infection is estimated at 40–100% of the population and is highest in countries of a low socioeconomic status. Furthermore, CMV causes the most common congenital infection in developed countries (0.2–2.5% of live births) [3,4,7,10,11,12]. The pathogenicity of CMV depends on the immune status of the infected person. The most common signs and symptoms in immunocompetent individuals include fever, pharyngitis and tonsilitis, lymphadenopathy, hepato- and splenomegaly (not as pronounced as in EBV infection), rash multiforme, headache and weakness. Rare manifestations of CMV infection in immunocompetent individuals include pneumonia, colitis, meningitis, Guillain-Barré syndrome, myocarditis and pericarditis. Laboratory tests typically reveal lymphocytosis with atypical lymphocytes (10–35%), elevated transaminases, hyperbilirubinaemia, haemolytic anaemia and thrombocytopenia. Congenital infection can occur both during pregnancy (transplacental infection) and during birth (infection by contact with cervicovaginal fluid or blood). The risk of transmission exists both in primary maternal infection and in viral reactivation or infection with a different strain. Primary infection is associated with the great risk of vertical transmission (average 30–40%), which increases in consecutive months of pregnancy. The clinical presentation is most severe when infection occurs in the first half of pregnancy (this results from the direct pathogenic impact of CMV on the foetus and from placental damage that decreases transplacental blood flow and causes secondary hypoxia). The symptoms of the disease are only manifested after birth in 10–15% of infected children, whereas 85–90% remain asymptomatic. The symptoms can appear several months or years later. The clinical presentation depends on the timepoint during pregnancy at which foetal infection occurred. Infection in the first or second trimester of pregnancy usually results in severe organ injury and in extreme cases may lead to miscarriage or intrauterine foetal death. It is acute, generalized and the most serious form of congenital CMV infection. The findings in the physical examination include hypotrophy, microcephaly, hepatosplenomegaly, petechiae, a "blueberry muffin"

rash, and muscle tone disorders or seizures. Infection in the second/third trimester of pregnancy mainly results in the "organ-related" clinical course of the disease and manifests as pneumonia, hepatitis, enteritis, chorioretinitis, myocarditis, aseptic meningitis or bone marrow involvement. Neonates infected in the third trimester of pregnancy tend to be asymptomatic after birth (asymptomatic congenital CMV infection) or present with a mild form of lymphadenopathy, hepatosplenomegaly, hepatitis or pneumonia. Severe long-term consequences, mainly progressive hearing loss (sensorineural in nature), vision disorders (abnormalities of the posterior eye segment, strabismus) and impaired development of mental and motor functions, occur in 5–15% of patients. The most common laboratory findings are anaemia, neutropenia, lymphocytosis or lymphopenia, thrombocytopenia, elevated aminotransferases (typically not higher than 200–300 IU/L; may persist for many weeks or months) as well as elevated alkaline phosphatase and γglutamyltransferase. Approximately 30% of neonates with hepatitis also have jaundice (increased concentrations of total and direct bilirubin). CSF findings usually show an elevated white blood cell count with a predominance of lymphocytes. In mild forms, each of these irregularities can be present as an isolated sign. Imaging abnormalities include CNS findings (lenticulostriate vasculopathy, calcification, ventriculomegaly, subependymal cysts, white matter lesions and brain developmental defects, and intracranial haemorrhage), hepato- and splenomegaly, ascites, echogenic bowel and generalized oedema. Perinatal infection may also occur while breast-feeding. It is estimated that the risk of this transmission is 58–69%. These infections are mostly asymptomatic or have a mild course [2,6,9,10,12,13]. The main diagnostic methods in CMV infection (congenital/acquired) include serology and molecular testing. The detection of the virus in urine or saliva using PCR in the first 21 days of the child's life is a "gold standard" in the diagnosis of congenital CMV infection. If the number of the virus copies in the urine exceeds 500 (0.5 × 103 copies/ml), it is indicated to extend the diagnostic process and test body fluids as well. Blood testing using this method should be treated as a supplementary examination since it is significantly less sensitive. The detection of CMV DNA in the CSF carries a poor prognosis. In immunocompetent individuals, infection usually resolves spontaneously. In the case of mononucleosis-like syndrome, the management is symptomatic [1,5,8,12,14]. None of the antiviral drugs currently used for adults in immunosuppression has been approved for the treatment of congenital cytomegalovirus infection in neonates. That is why treatment indications are determined individually. Candidates for therapy are neonates with a confirmed, symptomatic congenital CMV infection. Treatment should begin

as soon as possible after birth (within the first 28–30 days of life), and its duration depends on disease severity. The drug of choice is currently oral valganciclovir at a dose of 16 mg/kg every 12 hours (intravenous ganciclovir is used in patients who do not tolerate an oral form of the drug or with impaired intestinal absorption). According to international recommendations, it should last at least six weeks under the control of a serum drug concentration [1,8,12]. In the first case, a six-month-old child was referred to our department for an extended diagnosis following the detection of serology markers of CMV infection (IgM and IgG antibodies) and psychomotor retardation. Because of the child's age, the laboratory tests (blood PCR for CMV 1000 copies/ml, urine – a positive result) did not allow an unequivocal diagnosis of either a congenital or acquired infection, but the clinical presentation (lenticulostriate vasculopathy, psychomotor retardation and profound hearing loss) made a congenital infection highly probable. During hospitalisation, the girl was diagnosed with a transitional atrioventricular septal defect. The presence of this heart defect, which is associated with circulatory failure, was responsible for the signs and symptoms observed (lenticulostriate vasculopathy and psychomotor retardation), which is confirmed by the fact that these symptoms regressed after surgical correction of the cardiac defect [15,16]. The CMV infection was only a coincidence. Follow-up examinations revealed normal hearing parameters. In the second case, the 2.5-month-old boy was referred to hospital due to poor weight gain and significant anaemia. The entire clinical picture (diarrhoeal stools, fine papular skin lesions with signs of superinfection and a haemorrhagic component) and laboratory findings (positive anti-CMV IgM and IgG antibodies, positive urine PCR CMV test, anaemia, thrombocytopenia, elevated transaminases, signs of cholestasis, faecal occult blood) indeed indicated a symptomatic CMV infection, with the differentiation between a congenital or acquired infection being impossible. The meticulous diagnostic process led to the final diagnosis of classic cystic fibrosis. In this case the CMV infection was also a coincidence.

To sum up, CMV infection is a common infection. An extended diagnostic panel with CMV detection markers should be considered only in patients with immunodeficiency and in atypical, difficult situations. In a congenital CMV infection, laboratory irregularities and clinical signs and symptoms are similar to those seen in other TORCH infections, metabolic disorders, cardiac diseases, genetic conditions and sepsis. This has consequences in the form of the high probability of an overlap syndrome. In most cases, the detection of serological and molecular markers of infection at an age later than three weeks precludes the differentiation as to whether the infection is congenital or acquired. In each such case, one

should be very vigilant when conducting the diagnostic process and the test panel should be extended to include all diseases with a similar spectrum of clinical signs and symptoms.

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CASE REPORT

Cardiac tamponade due to anorexia nervosa in young women: A case study

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Abstract

Background: We present two cases of pericardiocentesis due to anorexia nervosa in young women.
Case description: A twenty-year-old and a twenty-four-year-old female with a history of ano-rexia nervosa were admitted to the cardiac surgery department due to pericardial effusions.
Discussion and evaluation: Both cases needed urgent pericardiectomy. Our patients did not show any signs of acute heart failure during the hospitalization. Due to their primary diagnosis, they needed psychological support and their food intake required monitoring.
Conclusions: Pericardial effusions are common in adolescent AN patients, and echocardiography monitoring is necessary to prevent the progression of acute cardiac tamponade.
Keywords: cardiac tamponade, anorexia nervosa, pericardiocentesis

Introduction

Anorexia nervosa (AN) is a significant medical and social problem affecting an increasing number of people. The risk factors are very often psychological, but the disease also manifests itself as a result of the fashion for a slim figure promoted in the media. The etiology of the disease is not fully understood, but research indicates that the pathogenesis of AN is multifactorial. The causes of the disease can be divided into factors that cause a predisposition to the disease, trigger the disease, and maintain the symptoms [1,2].

Anorexia nervosa leads to changes in all systems of the human body. The most common complications include growth disorders, osteoporosis, cessation of menstrual periods and sexual development, as well as neurological and cardiac problems. Anorexia nervosa is characterized by the highest mortality rate among psychiatric disorders, of which approximately one third of deaths are caused by complications of the cardiovascular system.

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The leading cause of hospitalization among AN patients is cardiovascular complications, which occur in up to 80% of cases and account for at least one third of all patient deaths [3]. Cardiovascular disorders occurring in the course of anorexia nervosa have a complex etiology. Protein deficiency and weight loss result in decreased heart muscle mass, hypercholesterolemia, and fluid accumulation in the pericardial sac. Long-term high cholesterol levels can cause the build-up of atherosclerotic plaques in the vessel walls, which increases the risk of atherosclerosis in later years. Accumulation of fluid in the pericardial sac requiring pericardiocentesis is described in the literature only casuistically [4,5], but statistics show that pericardial effusion develops in about 25% of individuals with AN [6]. The fluid accumulating in the pericardial cavity compresses the heart from the outside and prevents it from dilating properly, which contributes to the development of congestive heart failure. The reduction in heart muscle mass and the accompanying slower metabolism of cardiomyocytes lead to reduced contractility. Electrolyte deficiency, dehydration, and the use of pharmacological agents lead to hypotension and changes in the ion balance. The resulting consequences include cardiac arrhythmias and numerous complications outside the circulatory system [7].

Cardiac tamponade

Cardiac tamponade (pericardial tamponade) is a complex clinical symptom caused by excessive fluid accumulation in the pericardial sac, where the heart is anatomically located. Physiologically, the heart is surrounded by a serous membrane called the pericardium, and under normal conditions, around 30–35 ml of fluid is present. When tamponade occurs, a large amount of fluid or blood accumulates in the pericardial sac, up to about 2 litres. The result of the accumulated fluid creates pressure on the heart and impairs its work, especially in the diastolic, or filling, phase. As a result, blood ejection to the periphery is reduced, thereby reducing blood flow through the body, ultimately leading to organ and tissue hypoxia [8].

Risk factors

The incidence of pericardial effusion in the general population is unknown, while statistics conducted in the United States report about two cases per 10,000 people. It has been reported that about 2% of penetrating chest injuries end in cardiac tamponade [9]. However, there are subgroups of patients in whom pericardial effusion is more common. These include HIV-infected patients, patients with end-stage renal failure, patients with known or hidden malignancies, a history of congestive heart

failure, tuberculosis, autoimmune diseases such as lupus, and penetrating traumatic injury to the central chest.

The classic symptoms of cardiac tamponade consist of those that form the so-called Beck triad:

- low or paradoxical blood pressure (a drop in systolic pressure during inspiration of more than 10–15 mmHg);
- muffled heartbeat;
- excessively filled neck veins.

Treatment

As part of the treatment of tamponade, immediate pericardial puncture (pericardiocentesis) or cardiac surgery (pericardiectomy) is recommended to evacuate the fluid. Drainage from surgical access is indicated, for example, in cases of purulent pericarditis or emergencies when there is bleeding into the pericardial sac [8].

The purpose of this paper is to present two case reports of cardiac tamponade in patients with anorexia.

Case 1

A 20-year-old female patient was admitted from the Central Emergency Room for urgent decompression of cardiac tamponade of unknown etiology. A history of Turner syndrome, Crohn's disease, anorexia, and weight loss were noted. The patient was conscious and of sound mind. The patient was operated on under general anesthesia, and 75 ml of serous fluid under pressure was decompressed from the sub-sternal access. Fluid was collected for cytological and bacteriological examinations. A fragment of the pericardial sac was taken for histopathological examination. A drain was placed into the pericardial sac, which was removed with minimal drainage. In the echocardiographic examination, there was no recurrence of tamponade features. After the procedure, the patient was significantly weakened, but her cardiovascular and respiratory systems were stable. She refused to take hospital meals but agreed to take meals brought by her mother. During her stay on the ward, she reported persistent nausea. There was an episode of vomiting with clear gastric content. Anti-inflammatory treatment was started. Basic laboratory diagnostics were performed (Table 1). A histopathological examination showed no malignant tumour cells. In a bacteriological examination, the fluid was sterile after five days of culture under aerobic conditions. Her wounds were dry, and healing was normal. On the fourth day of her stay on the ward, the patient was transferred

in optimal general condition and in a stable cardiovascular and respiratory condition, for further diagnosis and inpatient treatment.

Psychiatric consultation:

Her BMI was around 16. A telephone interview with her mother revealed a restrictive eating disorder since 2017. The patient had been reluctant to seek treatment and was undergoing psychotherapeutic interventions. On examination, she was found to be auto- and allopsychically healthy. She declared herself to be in a neutral mood and expressed herself quietly. She overstated MS and perceived herself to be dysmorphic. She made a disturbing criticism of eating disorders and was incoherent. She reported periodic sleep disturbances. The recommendations were to continue psychotherapy and a prescription of mirtazapine 15 mg 0–0–1/2.

Diagnostic tests:

Echocardiography before surgery
Pericardial fluid was found mainly in the area of the right atrium and right ventricle, with modelling of the right heart cavities and features of tamponade. Variable tricuspid inflow was present. The morphology and function of the heart valves did not manifest significant abnormalities. EF was 60% without pleural fluid.

Echocardiography after surgery
There was no pericardial fluid. The ascending aorta was 2.8 cm. The right ventricle was 2.4 cm; the left ventricle 4.0 cm; the left atrium 2.5 cm. There were no valvular pathologies, although there was a slight thickening of the anterior mitral cusp. There were no regurgitations, and the transvalvular gradients were normal. The patient's LVEF was 60%, and IVC was 1.5 cm. There was no pleural fluid.

Echocardiography at discharge
There was no pericardial fluid nor valvular pathologies present. Her LVEF was 60%. There was no pleural fluid.

Chest X-ray
The cast of the lower fields showed shadows of the nipples. Her lungs were without infiltrative changes, and her diaphragm was free. Her heart and aorta were radiologically normal.

Case 2

A 24-year-old female patient presented to the Central Emergency Room for suspected "chronic pericardial tamponade". She had had no history of pericardial fluid for three years. On pre-admission, echocardiographic examination fluid was seen in the right ventricular region (up to 24 mm), with marked right atrial and right ventricular collapse; the left ventricular ejection fraction (LVEF) was 60%, and E/A ratio 2.5. An increase in pericardial fluid to 24 mm anterior to the right ventricle was noted, compared with the April 2023 study (20 mm) and July 2023 (18 mm). Her BMI was 13.7. The patient had had a history of anorexia for five years. The following concomitant abnormalities were present: protein-energy malnutrition, secondary amenorrhoea, history of depression, and oesophageal hiatal hernia. The patient was operated on under general anaesthesia, 250 ml of fluid was decompressed from a mini-access under the xiphoid process, leaving a drain, which was removed the next day. The fluid was sent for histopathological and bacteriological examination. The postoperative course and wound healing were without complications. The patient, who was in good general condition, was discharged from the Clinic on the third day after surgery with recommendations. Her histopathological examination showed no malignant tumour cells. In a bacteriological examination, the fluid was sterile under aerobic conditions after five days of culture.

Echocardiography before cardiac surgery

Figure 1 shows tamponade – parasternal long axis view (A); subcostal long axis view (B). Arrows indicate fluid accumulation.

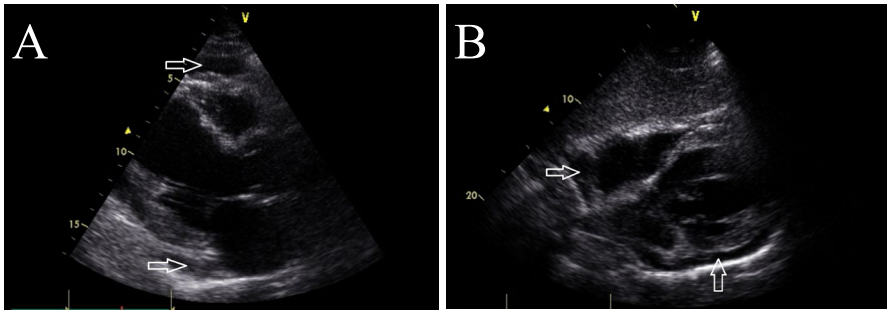

Figure 1. Echocardiography (A) pasternal (B) long axis view

Echocardiography after pericardiocentesis

No pericardial effusion. The left ventricle in the end-diastole is 4 cm, the right ventricle in the four-chamber view is 3 cm, and the ascending aorta is 3.4 cm. Heart valves have normal morphology and function. LVEF 65%, IVC 1.5 cm. No pleural effusion.

12-lead ECG tracings before operation

ECG findings: suggest sinus bradycardia with HR 45 bmp, beat-to-beat variation of PQ(PR) interval, with values changing from 80 to 160 ms (Figure 2A, 2B). Both findings are most probably attributed to impaired autonomic regulation and may correlate with malnutrition.

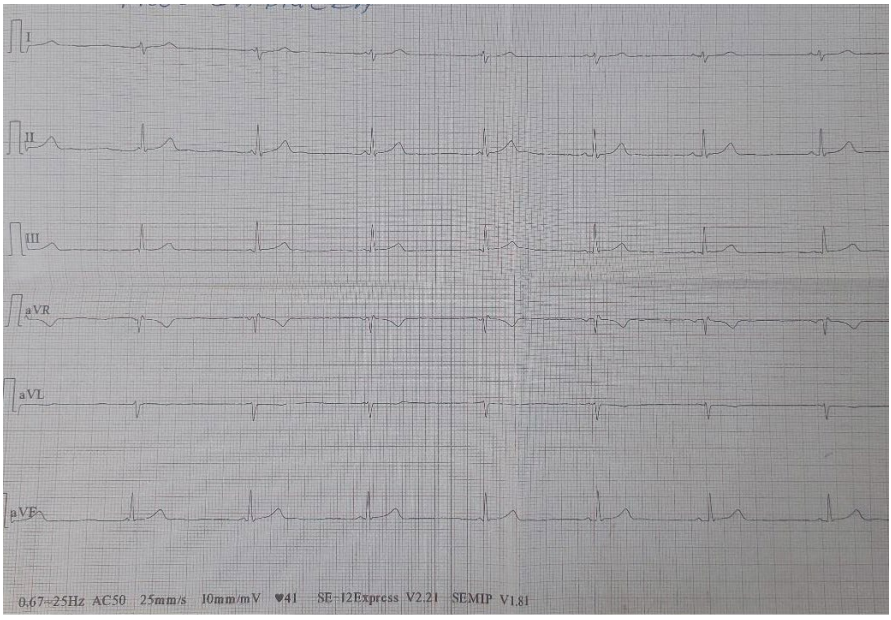

Figure 2 (A). 12-lead ECG

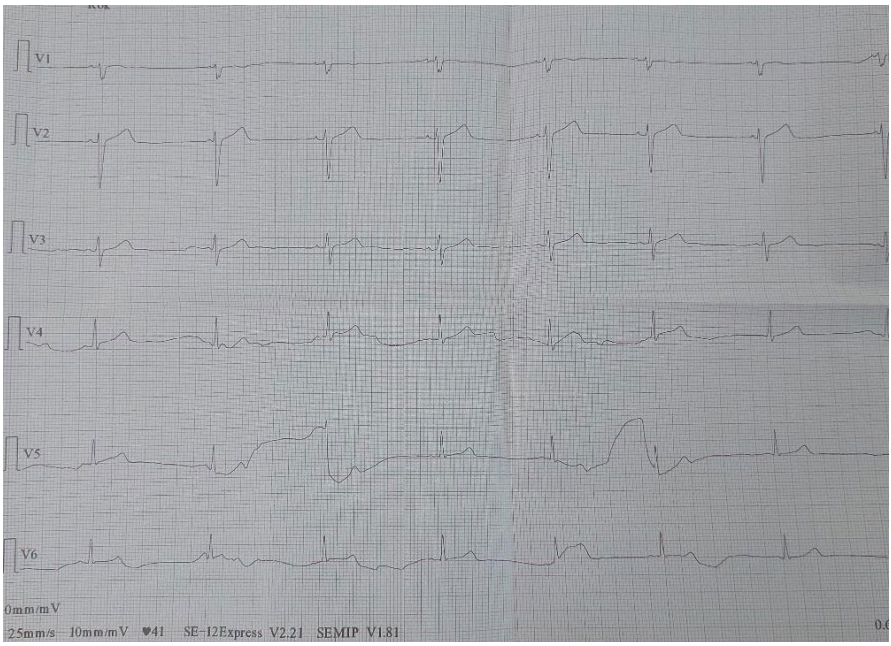

Figure 2 (B). 12-lead ECG

Chest X-ray

The heart silhouette and aorta are normal in size. The lung has no focal changes. The diaphragm has blurred outlines.

Psychological consultation

The patient received psychological care. A supportive interview was conducted. It was recommended that a psychiatric consultation be ordered to optimize treatment before the patient's discharge.

Clinical and Laboratory Findings

Comparison of admission and discharge characteristics of two patients with anorexia nervosa and cardiac tamponade is presented in Table 1.

Table 1. Patients' characteristics and laboratory findings

Type of test [reference ranges]	Case 1 Admission	Case 1 Discharge	Case 2 Admission	Case 2 Discharge
WBC 10^3/μL [3.80–10.00]	5.39	5.33	2.51	6.71
RBC 10^6/μL [3.70–5.10]	4.29	3.88	4.27	4.09
HGB g/dL [12.0–16.0]	13.2	12	13.5	12.9
Creatinine μmol/L [44–80]	49	46	74	70

Type of test [reference ranges]	Case 1 Admission	Case 1 Discharge	Case 2 Admission	Case 2 Discharge
Glucose mmol/L [3.90–5.50]	5.1	4.5	4.6	4.5
Serum urea mmol/L [2.8–8.1]	2.7	2.3		7.6
Serum ALB g/L [35.0–52.0]	50.8	34.4	46.2	37.9
Serum total protein (TP) g/L [64.0–83.0]	64	62.7	67.5	53.7
HCG mIU/mL Premenopausal women: ≤1 mlU/mL	7.8	5.2		
FT4 pmol/L [12.0–22.0]		24.03	11.22	
FT3 pmol/L [3.1–6.8]		4.74	1.46	
TSH µIU/mL [0.27–4.20]		3.450	2.490	
TIBC µmol/L [40.0–80.0]		38.7		
UIBC µmol/L [24.2–70.1]		34.6		
Fe µmol/L [5.8–34.5]		4.1		
TSat % [20–40]		11		
Ferritin µg/L [15.0–150.0]		129.1		
CHOL mmol/L [3.00–5.00]		2.55		
CRP mg/L [<5.0]	2.2	22.2	<0.6	1.4
Electrolytes Na mmol/L [136–145] K mmol/L [3.5–5.1]	 139 3.6	 140 4.4	 137 3.9	 136 4.4
Magnesium mmol/L [0.66–1.07]		0.75	0.66	
Serum inorganic phosphorus mmol/L [0.87–1.45]		0.94	1.24	
Alkaline phosphatase – ALP U/L [35–105]		44	35	
SBP/DPB [mmHg]	108/76	85/60	94/61	85/60
HR [bmp]	86	78	41	40
Weight [kg]	45	37.5	45	45.9
Height [cm]	155	155	181	181
BMI	18.73	15.60	13.74	14.01
Temperature [C]	37.2	36	36.1	36.7

Discussion

We have described two cases of cardiac tamponade as a rare complication of AN with significant haemodynamic compromise in a perioperative setting. Only a few reports have described acute AN-associated tamponade requiring pericardiocentesis [10]. In their systematic review, Sachs et al. concluded that pericardial effusion is generally a reversible, asymptomatic marker of disease severity. Furthermore, they recommend that echocardiography be considered a standard examination in those patients with severely reduced BMI [11]. In our patients, echocardiographic monitoring was crucial in the diagnosis of tamponade. In a systematic review and meta-analysis Smythe

et al. showed that anorexia nervosa increases the incidence of cardiac tamponade in comparison with healthy controls [6].

Cardiovascular complications of AN also include sinus bradycardia, hypotension, tachycardia, postural hypotension, impaired myocardial performance, pericardial effusion, mitral valve prolapse, and sudden death. ECG abnormalities in eating disorders (particularly anorexia) include bradycardia, low QRS, P and T wave voltages, ventricular tachyarrhythmia, non-specific ST-T changes, the presence of U waves, and prolongation of the QTc interval.

QTc interval prolongation does not necessarily reflect underlying biochemical abnormalities, and studies have demonstrated QTc interval prolongation in individuals with normal electrolyte levels and demonstrated no correlation between the BMI and QTc interval.

A comprehensive cardiovascular assessment and ECG should also be performed regularly to detect cardiovascular manifestations of refeeding syndrome [12]. ECG abnormalities were observed in Case 2. The ECG recording revealed sinus bradycardia with a heart rate of 41–48 bmp. Some patients rapidly develop peripheral oedema and cardiac failure, and this should be suspected in the presence of rapid weight gain. The risk of heart failure in refeeding syndrome is reduced by controlled, closely monitored refeeding.

Treatment of anorexia is a multi-stage, long-term process involving various consultants – an internist, a psychiatrist, a dietitian, a psychotherapist, and, depending on possible complications, a cardiologist and an endocrinologist. The main goal of treatment for anorexia nervosa is to restore normal body weight and treat the complications of long-term malnutrition, treat mental problems related to eating disorders, and work with a consultant to try to change the patient's way of thinking about and perception of their own body and improve relationships with other people [13].

When life-threatening complications such as cardiac tamponade occur, urgent hospitalization in a surgical ward is required. Patients who experience acute complications of the disease are often treated in a general ward with a mixed population. Individuals with eating disorders are subject to complex interplays, both medical and psychiatric, that require close observation and supervision to ensure patient safety and medical stability.

Conclusion

Cardiac tamponade is a life-threatening condition. If tamponade is suspected, diagnostic echocardiography and urgent hospitalization for fluid decompression are required. Treatment includes careful fluid resuscitation,

administration of inotropic drugs, and pericardiocentesis. Careful monitoring is essential to prevent sudden deterioration [14].

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CASE REPORT

Awake surgery for eloquent area glioma in a pregnant patient: a case report with 7-years follow up

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Abstract

Background: Awake glioma surgery in pregnant patients occurs rarely and is a huge challenge for the whole therapeutic team, requiring the cooperation of a neurosurgeon, an anaesthetist, a speech therapist and an obstetrician.
In this paper we present the case of a 31-year-old patient in 22 hbd with low grade glioma (LGG) of the left temporal lobe.
The patient was admitted to the outpatient clinic, having experienced transient speech disorders for about a week. An MRI examination revealed an extensive tumour in the left temporal region. The speech cortical centres were mapped using fMRI and the awake surgery was tailored. The surgery was performed under neuroleptanalgesia with dexmedetomidine and remifentanil and regional anaesthesia. The speech centres were located. The tumour was completely removed, revealing astrocytoma fibrillare WHO II. The patient's speech was continuously monitored, as well as the foetal vital functions. The course of the pregnancy was uneventful. In the 48th month after the first operation, the patient underwent a reoperation due to tumour recurrence with consecutive protonotherapy. Currently, 88 months after the first operation, the patient and child both remain in very good condition.
Conclusions: Few cases of glioma resection with intraoperative awakening in pregnant women have been described in the literature. The awake method seems to be an optimal treatment option.
Keywords: awake craniotomy, pregnancy, low grade glioma

Introduction

The coexistence of a primary brain tumour and pregnancy is rare and was estimated by Haas in 1986 to occur in 3–6/1,000,000 live births [1]. In recent studies, only case series are available and the incidence of primary brain tumours diagnosed during pregnancy is unknown [2–8]. In addition, there are no established treatment paths since they vary for every case, depending

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on the size of the tumour, potential histology, neurological symptoms and stage of pregnancy. Different options, including termination of pregnancy, premature caesarean section, close monitoring, surgical resection and/or radiotherapy, during or after pregnancy, are tailored to each patient [3,8]. Treatment of eloquent area tumours is even more challenging and requires e.g. intraoperative awakening and therefore the close cooperation between a neurosurgeon, an anaesthetist, a speech therapist and a gynaecologist. Currently, only a few cases of glioma resection in pregnant women, performed in awake surgery, have been described in the literature [9–14].

In this paper we present the case of a 31-year-old patient in 22nd week of gestation (hbd) with low grade glioma (LGG) of the left temporal lobe.

Case description

A 31-year-old pregnant woman in 22 hbd who had had transient motor speech disorders for about a week was admitted to an outpatient clinic. A brain MRI revealed an extensive tumour in the left temporal region with mass effect (Figure 1). The tumour was hypointense in the T1-weighted sequence and hyperintense in the T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, with medium contrast enhancement and no diffusion restriction.

Due to the suspicion (suggested by the radiology consultant) of a possible high grade glioma and mass effect, surgery was recommended. The location of the speech cortical centres was mapped using fMRI and the awake surgery was tailored. The aim of the procedure was complete resection of the tumour, sparing speech function, while maintaining the safety of the pregnancy. The patient was fully informed about what to expect during the procedure.

The surgery was performed under neuroleptanalgesia with dexmedetomidine and remifentanil and regional anesthesia: ropivacaine and lidocaine. Sedation was controlled using the bispectral index (BIS) and EEG monitoring. The patient was in a semilateral position to prevent aortocaval compression. She was conscious throughout the entire surgical procedure with short periods of minor sedation for comfort during e.g. pinning, catheterisation or drilling. Magnesium was administered promptly before surgery. Sensorimotor monitoring was conducted. During the procedure the speech centres were located, safety margins were marked and the tumour was completely removed using a Cavitational Ultrasonic Surgical Aspirator (CUSA) in a piecemeal method.

In histopathology, a diagnosis of astrocytoma fibrillare (WHO gradeII) was made (WHO 2016 classification). The speech was continuously

monitored by the speech therapist. The vital functions of the foetus were checked by the gynaecologist. No abnormalities were detected in the postoperative foetal ultrasound. The patient was discharged on the fifth postoperative day in very good condition, with minimal reversable speech disturbances while speaking fast.

The further course of the pregnancy was uneventful and terminated on time (37 Hbd) by caesarean section due to the glioma diagnosis. The newborn was healthy. In the patient, all the speech disturbances had been resolved by the time of the birth. The patient was observed in the outpatient clinic and underwent a series of annual brain MRI scans.

Forty-six months after the first operation, the patient started to complain of stuttering when speaking and reported difficulties with word recall. An MRI scan revealed the recurrence of an exophytic tumour and post-contrast enhancement in one of the walls of the postsurgical cavity. Two months later (48th month) she underwent a reoperation, under general anaesthesia. Total excision was performed. There was no change in tumour histology in comparison to the first resection (astrocytoma fibrillare WHO II). Nevertheless, the oncologist referred the patient for protonotherapy, the course of which was uneventful.

In consecutive MRIs no recurrence of the tumour was found. Currently, 88 months after the first operation, the patient remains in very good condition. She complains of difficulties with finding words while speaking fast or under pressure. In everyday speech there is no noticeable deficit. Her 7-year-old child is developing well, with no neurological, health or developmental issues noted since birth. In the patient's opinion, no difference between her child and peers may be found.

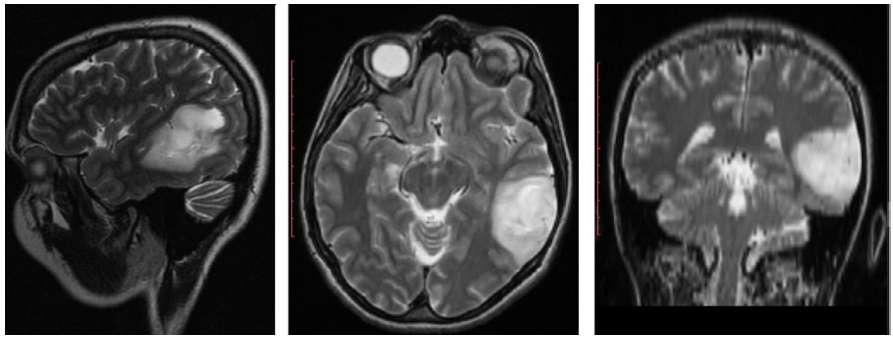

Figure 1. Preoperative MRI with left temporal lobe glioma T2 images

Discussion

Gliomas in eloquent areas of the brain pose a significant challenge due to the risk of postoperative deficits. Pregnancy further complicates management, considering the potential risk to the mother and foetus. The impact of pregnancy on glioma prognosis is inconclusive. Some authors consider the direct association between pregnancy, overall survival and tumour recurrence to be doubtful [4,7,8], whereas others point to the adverse effects of pregnancy on neoplasm [2,3,6,15]. Determining the prognostic impact of pregnancy, especially in LGG, is challenging. Pregnant patients with glioma can be divided into two groups: those newly diagnosed while pregnant and those whose tumour is diagnosed before conception [3,7]. Management, history and prognosis are different in these groups and depend on the exact histopathology, the occurrence of seizures, tumour volume, oncological treatment, recurrence, clinical deterioration and the molecular profile of the tumour [3,7,8]. Treatment varies significantly and must be tailored to each patient individually. In the first trimester or the early part of the second one termination is a possible option [3,5,8]. When maintaining pregnancy, management becomes particularly difficult due to the adverse effects of pregnancy itself (caused by hormonal and haemodynamic changes and increased levels of growth and angiogenic factors) and the wellbeing of the foetus [3,5,8,16]. In stable patients with favourable histology, expectant management until the end of the pregnancy is possible, otherwise appropriate surgical and/or radiotherapeutic and/or chemotherapeutic treatment is implemented [6,8,17]. For resection, the second trimester seems to be optimal [16,18]. Careful MRI monitoring should be performed, which impacts treatment options [3,5]. Rigorous obstetric supervision throughout the whole pregnancy is advisable [2,5].

Additional complications occur with eloquent area tumour location, where progression or resection may cause major deficits. Awake craniotomy allows real-time mapping and the preservation of critical brain functions, which is crucial in eloquent area glioma [19]. It encourages a maximal safe resection, which is crucial in terms of overall survival in glioma patients [20,21]. So far, only the safety of surgery during pregnancy under general anesthesia has been investigated. Recently, there have been single reports of successfully performed awake glioma resections in pregnant patients [9–11, 13,14,17,19,22,23] and one systematic review by Mofatteh et al. [12]. Maintaining optimal neurological health in the pregnant patient is crucial due to the future need to fulfill parental responsibilities [12]. Awake craniotomy protocol reduces exposure to the anaesthetic medication usually used in general anaesthesia [12], which could cause some harm [5,8,11,16,17,19,23]. In

awake procedures intravenous sedatives are used in addition to local anaesthesia, which plays the main role, thus diminishing the usage of intravenous drugs [12]. The potential adverse effects of sedative drugs on the foetus occur rarely and beneficial effects, when applied at appropriate concentrations, have been reported [5,8,11,16,17,22]. In the review by Mofatteh et al., propofol was used in five out of nine studies; dexmetomidine in five out of nine, remifentanil or fentanyl in eight out of nine, lignocaine plus bupivacaine in three out of nine and lignocaine plus ropivacaine in three out of nine; in one study sevoflurane was administered [23] with no adverse effects to the foetus or mother reported, despite the drug regimen. However, the foetus should be thoroughly monitored pre-, intra- and postoperatively [10–12,24].

Awake craniotomy in pregnant women requires the multidisciplinary cooperation of a neurosurgeon, an obstetrician, a speech therapist and an anaesthetist. Proper preparation for complications such as intraoperative seizures, agitation, the need for urgent intubation, complications with foetus, and even emergent caesarean section, seem to be crucial and alternative plans/scenarios should be elaborated [11–13,25]. The patient's resilience, compliance to procedures, proper preparation and cooperation with the whole surgical team are essential.

Due to the low incidence of gliomas in pregnancy, there are insufficient guidelines for treatment using various methods tailored to individual needs. Current reports of awake surgery in pregnant patients are rare and concern various histopathological cases [12]. Moreover, in recently published reports there is a lack of long-term follow up of patients and their children to investigate the consequences of glioma surgery during pregnancy using awake craniotomy. In our case, a 7-year follow up provides us with a thorough insight into the long-term effects on both mother and child, giving hope for high efficacy and the long-term safety of awake craniotomy during pregnancy for glioma surgery in eloquent areas.

Conclusions

Glioma in pregnancy remains a rare condition in neurosurgical practice. Nevertheless, due to the double risk for both the mother and the foetus, it is an urgent matter that needs to be resolved. Different aspects of treatment have been discussed in the literature including the necessity to perform awake resections. Unfortunately, due to the rarity of cases, there is still a lack of evidence to inform the guidelines. Nevertheless, the awake-awake-awake method seems to be a viable option for eloquent area glioma resections in pregnant patients, offering favourable long-term

outcomes for the woman and her child. This case underscores the importance of planning individualised treatment and comprehensive follow-up in managing such complex cases. Precise guidelines on pre-, intra- and postoperative treatment should be developed.

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CASE REPORT

Neonatal neuroblastoma

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: Neuroblastoma is the most common malignant tumor occurring in early childhood. Most of them are located in the adrenal glands. Extra-adrenal localization is rare.
Case description: In this paper, we present a case of congenital neuroblastoma, which was identified in the neonatal period. The tumor was located in the posterior mediastinum in the paravertebral region.
Discussion and evaluation: It was not identified in the prenatal period and did not cause displacement of the thoracic organs. In this article, we provide obstetric, neonatal and pathomorphological descriptions from the autopsy.
Conclusions: We emphasize the need for screening ultrasound examinations in newborns.
Keywords: NB, congenital neuroblastoma, neonatal neuroblastoma, extra-adrenal neuroblastoma

Introduction

In this article we present a congenital neuroblastoma in an unusual, extra-adrenal location. The tumour was detected by chance in the first week of life. The newborn suffered from respiratory failure. The condition of the newborn prevented early diagnosis and treatment of the tumour. We describe atypical symptoms that are not commonly seen in neuroblastoma (e.g., atypical changes in vital signs, atypical test results) and which occurred in the patient.

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Obstetric case description, interview

The patient was 26 years old, healthy, and had no systemic diseases. Pregnancy was confirmed in the seventh week of gestation. The course of pregnancy was uncomplicated. The patient underwent ultrasound diagnostics in the first trimester of pregnancy. The examination showed a low risk of genetic defects. 20-week ultrasound examination confirmed a healthy male foetus with normal growth. The patient made nine gynaecological visits during the entire pregnancy. At each of them, the patient's blood pressure was measured (without deviations from the norm), the body weight was measured (normal growth), the patient was examined transvaginally and an ultrasound was performed. A physiological increase in foetal weight was observed; the umbilical cord and middle cerebral artery flows were within the norm, no abnormal or suspicious changes were visualized, and the image of the abdominal and thoracic organs did not deviate from the norm, with no displacements. The laboratory tests were as follows. Virological tests: HbsAg negative; VDRL: negative; AntiHCV: negative; tests for toxoplasmosis and cytomegalovirus infection: negative, and the result of a TSH performed at the beginning of pregnancy was 1.875. Gestational diabetes was also excluded. The last visit to the gynaecologist's office took place in the 37th week of pregnancy. On the day of the visit the patient weighed 89 kg and her RR was 142/94 mmHg, in laboratory tests: Hb 12.3 g/dl, PLT 155 thousand/mm3. A microscopic examination of the urine revealed numerous bacteria and leukocytes: 10–20 in the FOV. A bacteriological culture of urine was ordered and the result was negative (no growth of bacteria). Foetal movements were strongly felt by the patient. The ultrasound examination revealed a single live male foetus in the cephalic position, the EFW was 3290 g, AFI 10 cm, the placenta was located on the posterior wall, and the umbilical artery flows were as follows: PI=0.79, RI=0.56, S/D=2.26. Four days later the patient was admitted to hospital due to decreased foetal movements. RR during admission to the hospital was 122/82 mmHg and her temperature 36.8 degrees C. The CTG performed revealed foetal tachycardia and the patient was qualified for a caesarean section. The male newborn weighed 3640 g and was 55 cm long.

Case description of a newborn

The newborn was male and born at 37 weeks of gestation by caesarean section due to impending asphyxia. He had foetal tachycardia and on the day of delivery he had weakly detectable foetal movements, assessed on the Apgar scale at 9, 10 and 10 points respectively at 1, 5 and 10 minutes, with a body weight of 3640 g (LGA 90–97 percentile). The mother had HBs(-);

GBS(-); HIV(-). After birth, the child was crying, with a normal heart rate and pale pink skin. The results of cord blood gasometry were pH: 7.31; pCO2: 47.3 mmHg; BE: -2.48 mmol/l; Lactate: 4.1 mmol/l. Prophylactic procedures were performed (Vit K was administered and Crede's procedure was performed). From the 12th minute of life, the heart rate increased to 190–210/min., the ECG showed sinus tachycardia and respiratory difficulties appeared – CPAP breathing support was used with FiO2 0.21. The results of the control gasometric test were pH: 6.96; pCO2: 53.9 mmHg; BE: -19.8 mmol/l; Lactate 12.7 mmol/l. The boy was transferred to the neonatal intensive care unit. Monitoring of brain activity using aEEG was initiated. Central catheters (UVC, UAC) were inserted under ultrasound control. Direct measurement of blood pressure was started (mean pressure oscillated at 50–55 mmHg). Additional tests showed signs of anemization and a four-fold increased level of ammonia. In the CNS ultrasound examination, a blurred image of brain tissue was accompanied by an abnormal aEEG recording (extended, without sleep/wake rhythm). Due to the suspicion of intrauterine hypoxia, therapeutic whole-body hypothermia was initiated. Red blood cell concentrate was urgently transfused, blood culture was secured, and empirical antibiotic therapy, morphine analgesia sedation and parenteral nutrition were initiated. Functional echocardiography revealed signs of increased pulmonary resistance, and lung ultrasound (assessed through anterior and lateral access to the chest) showed a dominance of A-line artifacts. The newborn was intubated – mechanical ventilation was initiated in SIMV mode with FiO2 0.21. Despite the initially small improvement (reduction of base deficit, increase in peripheral perfusion, normalization of ammonia level), organ function disorders were still observed and the newborn required multidirectional measures: the circulatory system was supported with an infusion of pressor amines, blood products were transfused (red blood cell concentrate five times, fresh frozen plasma four times and platelet concentrate twice), electrolyte levels were supplemented (ion disorders), and due to weakening diuresis and then anuria, diuretics were administered.

On the second day, due to increasing circulatory failure (increasing pulmonary resistance, renal failure and increasing edema), oscillatory ventilation mode was used and inhaled nitric oxide (iNO) therapy was started, hydrocortisone was introduced into the treatment and diuretic therapy was intensified. After obtaining information about the colonization of the mother's genital tract by *Klebsiella pneumoniae* bacteria, antibiotic therapy was modified; according to the antibiogram, Meropenem was added.

On the second day, a lung ultrasound performed revealed a solid structure measuring 2 × 2.4 × 3.9 cm on the left paravertebral side. The lesion

was richly vascularized on the periphery. Pleura sliding was observed over the tumour (Figure 1 A and B). This was likely a proliferative lesion, warranting further imaging diagnostics. An CNS ultrasound showed signs of reperfusion. Blood gasometry showed persistent and worsening metabolic acidosis despite therapy, as well as progressive multiorgan failure and severe oedema. Despite multidirectional actions, the patient's condition did not stabilize. Death occurred after less than 6 days of treatment.

The autopsy examination supplemented the diagnosis of the lesion visible in ultrasound at the base of the left lung with neuroblastoma.

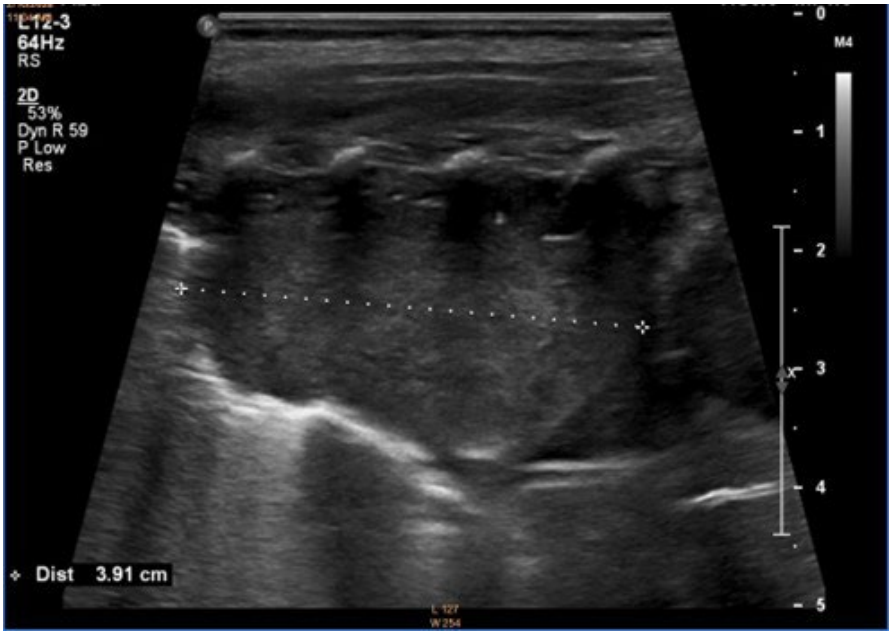

Figure 1A. The solid structure revealed in lung ultrasound

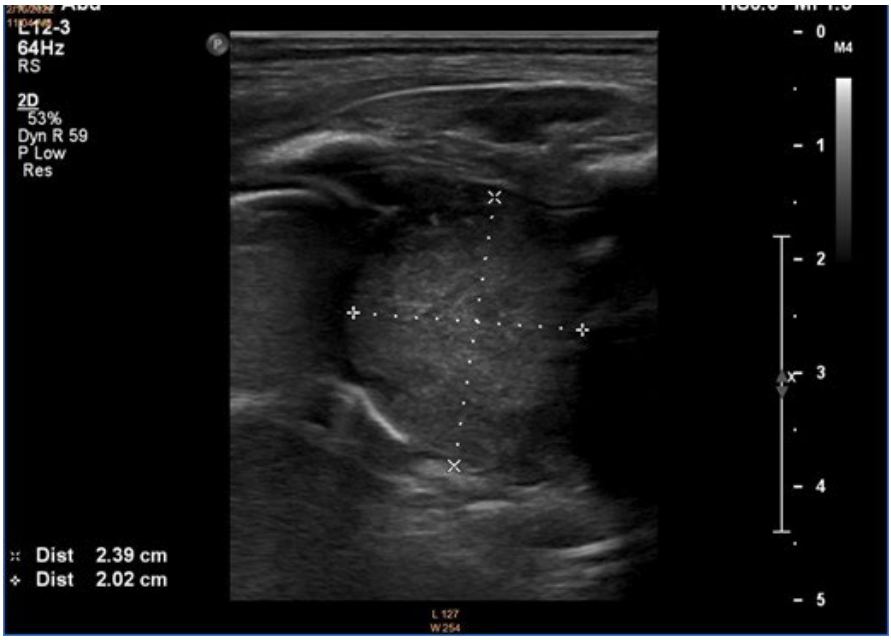

Figure 1B. The solid structure revealed in lung ultrasound

Pathomorphological case description

The autopsy was performed 68 hours after death. A tumour measuring 50 × 30 × 20 mm was found. It was located in the posterior mediastinum, in a paravertebral position. A histopathological examination confirmed neuroblastoma, a malignant small round cell tumour, of an undifferentiated type and encapsulated. In addition, the following were found: infant respiratory distress syndrome, massive pulmonary oedema and congestion, massive fibrin deposits in the lumen of the bronchioles closing their lumen, congestion of the myocardium and epicardium, congestion of the brain and cerebellum, congestion of the meninges, microthromboses in the cerebral vessels and in the vessels of the brain stem, a focus of foetal erythropoiesis in the liver, hepatic congestion, congestion of the thyroid gland, thymus, haemorrhagic necrosis of the renal medulla and ischemia of the renal cortex, congestion of the adrenal medulla with a focus of necrosis, a fibrinous thrombus in the umbilical arterial vessel closing the lumen, inflammatory infiltrates of lymphoblasts and neutrophils present in the lumen of the umbilical vessels, congestion of the wall of the small and large intestine, massive congestion and signs of incipient autolysis of the spleen, and congestion of the pancreas.

On the basis of clinical data in combination with autopsy data, supported by histopathological examination of the collected samples, the main cause of death of the newborn was determined to be the presence of a neuroblastoma tumour located in the posterior mediastinum. Tumours located in the chest in a paravertebral position may cause respiratory disorders or superior vena cava syndrome. These tumours are a source of catecholamines and may therefore cause tachycardia or hypertension and heart rate disorders, which could contribute to terminal respiratory and circulatory failure.

Discussion

Neuroblastoma (NB) is a childhood cancer. It is diagnosed in 10.5/1 million children per year [1]. It originates from neural crest cells (NCC), which are a transient population of multipotent cells. NCCs migrate from the neural plate border to target sites where they differentiate into different tissue types. Neuroblastoma occurs when NCC cells undergo defective differentiation due to, for example, genomic or epigenetic disorders. This mechanism explains why NB can arise in various locations, but the most common locations are the adrenal glands and paraspinal ganglia. NB is characterized by an early age of disease onset, a high rate of metastasis at diagnosis, and a tendency for spontaneous regression of tumours in infancy [2]. NB accounts for approximately 10% of all childhood cancers [3]. It is the most common malignant tumour in infants and most of them are small tumours located in the adrenal glands [4]. In the case of our patient, the tumour was located in the paraspinal region in the chest. This is an unusual location and is rarely seen. Giglioti et al. report that only 7.5% of neonatal NBs were located in the thoracic cavity [5]. Evans also describes two neonates with prevertebral NB. The neonates described died of respiratory failure [6]. The literature also describes cases of prevertebral NB in foetuses that died during pregnancy [7]. A similar localization is described by Moppett et al. in two patients out of all 33 cases of NB detected between 1986 and 1994. In these patients, the tumour was located, as in our patient, in a paravertebral position. In both patients, the tumours were detected in the neonatal period after the onset of respiratory failure symptoms. The patients were treated surgically. The patients also had comorbidities with complications such as abnormal sweating and flaccid paralysis of the lower limbs [8]. Our patient did not experience other accompanying symptoms that may occur in patients with neuroblastoma, such as excessive sweating and flaccid paralysis of the lower limbs. There was no pleural effusion [9]. Other visible symptoms accompanying NB may include a berry rash and subcutaneous skin nodules [10]. Our patient did not experience any of the above. Symptoms

of NB depend on the location of the primary tumour and the presence of paraneoplastic or metastatic syndromes. The most frequently described symptoms of NB in newborns and small children are lethargy, irritability, eating problems (lack of appetite), swallowing problems, vomiting, defaecation problems (constipation), abdominal enlargement, and abdominal pain. NB are often incidentally detected tumours. Our patient did not demonstrate any of these symptoms. The patient's main complaint was respiratory failure. Evans, in his description of five cases of posthumously diagnosed NB, writes about respiratory failure. He also describes the occurrence of anaemia in one of the children, similarly to our patient [6].

In the cases described, a case of acute shock in a newborn child was found, which occurred in the first hour of the child's life. In this case, shock was diagnosed and the child received treatment (chemotherapy) [11]. Neuroblastoma can also occur in utero. Harvey and Grey describe a paravertebral NB in a macerated foetus [12].

90% of NB tumours produce catecholamines and therefore the diagnosis is made on the basis of the results of biochemical tests (determination of catecholamines and their metabolites in a 24-hour urine collection or in a single test) in combination with imaging studies and histological analysis. The most commonly used tests are VMA (vanillylmandelic acid) and HVA (homovanillic acid), which have a sensitivity of 81.6% and 80.5%, respectively. Better results are obtained in the presence of metastatic disease (sensitivity 100%, specificity 99.7%). There is evidence that the combination of NMN (normatenephrine) with VMA or HVA improves diagnostic efficiency, while the inclusion of 3-methoxytyramine increases diagnostic sensitivity to 95%. In the case of our patient and his serious general condition, it was not possible to perform a quick diagnosis [13–15].

The definition of congenital NBL is neuroblastoma detected prenatally or within 28 days of birth. Since our patient's tumour was diagnosed in the first week of life, we can speak of congenital NB. Congenital tumours constitute 5% of all NB cases diagnosed annually and most cases are diagnosed in the first month after birth [14].

In the Italian registry, Gigliotti et al. report that only 20% of NB cases, regardless of location, were detected prenatally [5]. NB detected prenatally at 30 weeks of pregnancy is described by Park et al. The tumour was located on the right side of the chest and was accompanied by a pleural effusion in the right pleura, which made diagnostics easier [9].

The incidence is slightly increased in males (1.2:1) [16]. This was also the case with our patient.

A high rate of spontaneous regression has been observed in infants with NB. Investigators such as Holgersen et al., Acharya et al., Sauvat et al. and

Oue et al. have observed spontaneous regression of adrenal tumours that were diagnosed prenatally. There is also evidence of spontaneous regression of tumours detected in population-based NB screening programs [17–20]. In our patient, due to the rapidly progressing deterioration of his general condition, no tumour regression was observed; on the contrary, on the second day of life the dimensions of the tumour in the ultrasound examination were 2 × 2.4 × 3.9 cm, while in the autopsy examination they were already: 2 × 3 × 5 cm.

Kerbl et al. did not observe spontaneous tumour regression in his patients. He described cases of congenital NB in four patients; one patient's tumor was detected prenatally and the other three in the first weeks of life. In all four cases, the tumours were located in the adrenal glands. Kerbl reports that neither noninvasive nor invasive tests were able to predict tumour behaviour. Kerbl et al. conclude that a general "wait and see" strategy cannot be recommended for patients with early and incidentally detected NB [21].

In our patient, due to his poor general condition, the need to stabilize the vital parameters came to the fore. It was not possible to perform imaging tests such as computed tomography or magnetic resonance imaging. The only imaging diagnostics was ultrasonography and it was adjusted to the child's condition. The images presented in Figures 1 and 2 were taken in the sagittal and transverse planes, showing the paravertebral region on the left side in the thoracic section. Histopathological diagnosis was not possible during his lifetime, thus implementation of a treatment plan was also unlikely. Due to the patient's death on the 6th day of life, diagnosis was provided posthumously.

In children with good performance status, Maris et al. report that approximately half of all cases are now classified as high-risk tumours, and overall survival rates are less than 40%, despite intensive multimodal therapy [3].

In the International Neuroblastoma Risk Group (INRG), an analytical cohort of 8800 patients, the proportion was fairly evenly distributed between North America (48%) and Europe (47%), as well as patients from Japan (5%). According to INRG, the overall 5-year EFS (event-free survival) and OS (overall survival) rates were 63% ± 1% and 70% ± 1%, respectively, with a median follow-up of 5.2 years in 5819 patients alive without disease relapse [22].

The standard treatment is surgical resection, which gives excellent overall results, or chemotherapy [11,23].

Conclusions

The increasing quality of ultrasound diagnostics during prenatal examinations does not reduce the need for postnatal ultrasound diagnostics.

It is important to remember that NB may be extra-adrenal.

Analysis of catecholamine metabolites in 24-hour urine samples is helpful in making a diagnosis in paediatric patients. In such young patients as ours with multi-organ failure, it is difficult to obtain a sufficient amount of urine. However, using an indicator calculated on the basis of creatinine clearance, for which we can use a single urine collection, is associated with a measurement error dependent on muscle mass.

We cannot conclude that NB was the cause of the poor condition of the newborn, because due to his rapidly deteriorating condition and unstable situation, it was not possible to undertake diagnostic and therapeutic procedures for the mediastinal tumour. It is also possible that the tumour contributed to the general condition and eventual death of the newborn.

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