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Arteriovenous Malformation (AVM)-A Possible Cause of Outbreak

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Abstract

The chance of being born with a life-threatening arteriovenous malformation is only one in a thousand worldwide. Due to the rarity of the neurological disease, it does not appear to be a lucrative area of research. That is why only little new progresses has been made in understanding and combating the causes of the vascular anomalie.

After a Magnetic Resonance Imaging (MRI) at the Charitè Berlin on February 20, 2023, a thirty-year-old Arteriovenous Malformation (AVM) patient received the possible diagnosis of an AVM in the cerebellum in the well-known and usual cranial fossa in the brainstem of the choroid plexus after his cerebral hemorrhage in 2011. Without much understanding of the cause of the onset of the disease, the patient received a recommendation for a dangerous, risky and difficult angiographic procedure for the second time.

Since genetic and external influences during pregnancy play a role in an arteriovenous malformation, the disease must be viewed not only from an expert neuroradiological and neurosurgical perspective, but also with an all-encompassing familial, medical and histological understanding. Therefore, relevant processes of the patient from his mother's pregnancy to the current point in time were reflected and scientifically combined with diseases of his ancestors.

In this literature review, the reason for the rare disease is sought, researched and sensibly combined using seven specialist literatures. A new possible cause for the rare disease was found.

Keywords: Nitrosamines • Neural ear defect • Spina bifida • Congenital arteriovenous fistula • Formaldehyde • Lymphatic organs • Epithelium • Capillary endothelium • Circumventricular organs • Lymphoepithelial organ • Involution • Erythrodiapedesis

Introduction

Information about the anamnesis

Since the disease arteriovenous malformation is a possible genetic disease, several people and their behavior must be described.

B. Maier-mother of F. Maier, AVM patient

Maier was born on February 11, 1961. Shortly after she received the doctor's congratulations on her pregnancy, she ate a large portion of sauerkraut and a pretzel with Nutella.

Mother's brother

The mother's brother (17 years old) died at the age of thirteen from leukemia or heart failure after an examination within a week of diagnosis.

Grandparents

The AVM patient's maternal grandfather died of prostate cancer in 2001. During the course of chemotherapy, he was unable to empty his bladder.

Great aunt

The AVM patient's maternal great-aunt died of a pulmonary embolism in 1992.

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F. Maier-AVM patient

He was born in October 19, 1992 and lived with his parents and his sister in the small town until he fell ill. In his free time he enjoyed playing tennis and drums. He was also interested in Internet and computer technology. After graduating from high school in 2009, he began training as an office clerk in a car dealership. At the time of the accident and diagnosis, F was in his second year of training. On January 10, 2011, Mr. Maier began his daily commute to the car dealership. He was traveling on his bike. On the way there, F suddenly felt a headache, nausea and vomited. After he was able to draw attention to himself at a traffic light, passers-by called an ambulance, which took him to the Memmingen Clinic. In the emergency room there, a cerebellar hemorrhage was diagnosed using computer tomography. He was then immediately transferred to the neurosurgical department of the Augsburg University Hospital for an emergency operation. After two further operations and subsequent acute intensive care treatment at the Augsburg University Hospital, F was transferred to the neurological rehabilitation clinic "Schlossklinik Bad Buchau" on February 11, 2011. This was also followed by an inpatient medical neurological rehabilitation from May 23, 2012 to June 22, 2012 in the Hegau Youth Center and an inpatient medical-vocational rehabilitation from July 2, 2012 to August 10, 2012 in the same neurological hospital and rehabilitation center. In addition, another inpatient rehabilitation stay in phase D took place from July 8, 2015 to August 12, 2015 in the Enzensberg specialist clinic. As part of a follow-up check in October 2016, another AV fistula was discovered, which led to another angiography.

Terminology

Arteriovenous (AV) fistula: An arteriovenous fistula is a short connection between an artery and a vein. The blood does not flow out of the artery *via* the fine capillaries, but instead reaches the draining vein at high pressure. The vessel is overloaded and can bulge. In addition, the tissue below the bypassed capillaries does not receive enough blood. In general, a fistula is an unnatural passage between organs, vessels or tissues that normally does not belong there. The AV fistula does not always need to be treated. Small fistulas between arteries and veins usually do not cause any symptoms. If impairments do occur, the unnatural connection is closed using embolization or removed during surgery. There are also some risk factors that may promote arteriovenous fistulas. These include, for example: Diagnostic and therapeutic procedures such as a cardiac catheter-especially if the procedure affects the blood vessels in the groin, certain medications, for example blood thinners (anticoagulants) or antifibrinolytics, which inhibit the dissolution of fibrin and counteract blood loss., high blood pressure (hypertension), High Body Mass Index (BMI) with severe overweight and obesity (obesity), older age [1]. With congenital AV fistulas, babies are born with the arteriovenous fistula. There is a defect in vascular development in the womb. AV fistulas naturally affect younger people. Otherwise, the AV fistula can in principle occur at any age. Dural Arteriovenous Fistula (dAVF) is one of the most common causes of pulse-synchronous tinnitus. Dural AV fistulas are short-circuiting connections between an artery and a vein on the hard meninges (dura mater). They are not static lesions. Spontaneous regression and healing are possible, but rare.

Arteriovenous Malformations (AVM): Arteriovenous Malformations (AVMs) are short-circuit connections between arteries and veins supplying the brain, which result in the formation of a highly perfused tangle of vessels. An arteriovenous malformation can in principle occur anywhere in the body, but is of particular importance in the brain due to the surrounding brain structures, the possible symptoms and the risk of bleeding. AVMs can change over the course of life, which can also change the symptoms and the risk of bleeding. Often, arteriovenous malformations are asymptomatic and are discovered incidentally on a CT or MRI of the brain. However, AVMs can also cause symptoms, most commonly headaches or seizures. Due to increased blood flow, AVMs can draw blood away from healthy brain tissue (so-called steal effect), causing a stroke. There is also a risk that an AVM will rupture and lead to a life-threatening cerebral hemorrhage. Because of these diverse symptoms, it makes sense to treat an AVM in many cases.

Literature Review

Theoretical basis and possible prerequisites for the development of a congenital AV fistula

Chemical reactions containing nitrates: The nitrate content in plants does not solely depend on fertilization. There are vegetables that store nitrate, while other varieties have little tendency to accumulate. Leaf and root vegetables in particular, such as lettuce, lamb's lettuce, chard, spinach, radishes, radishes, beetroot and especially rocket, sometimes have high nitrate concentrations (nitrate values of well over 1,000 mg/kg). In comparison, fruit vegetables (e.g., tomatoes, peppers, cucumbers, beans or peas) only have a relatively low nitrate content (below 500 mg/kg) (Table 1).

High: 1,000-4,000 mg/kg nitrate	Medium: 1,000-500 mg/kg nitrate	Low: below 500 mg/kg nitrate
Leafy vegetables: Lettuce, endive, ice cream lettuce, lamb's lettuce, spinach, Swiss chard, rocket	Root and tuber vegetables: Carrots, kohlrabi, celery	Fruit vegetables: Peas, cucumbers, green beans, peppers, tomatoes
Brassica vegetables: kale, Chinese cabbage, white cabbage, savoy cabbage	Brassica vegetables: cauliflower, cabbage	Brassica vegetables: Brussels sprouts
Root vegetables: beets, radishes, radishes	Onion vegetables: leeks	Onion vegetables garlic onions
	Fruit vegetables: eggplant, zucchini	Fruit, cereals, potatoes

Table 1. Differences in the nitrate content of fruits and vegetables.

The first column from the left lists fruits and vegetables that have a high nitrate content (1,000-4,000 mg/kg)-sauerkraut=white cabbage. In the middle column, fruits and vegetables with a nitrate content of 1,000-500 mg/kg are mentioned and in the right column from the left are fruits and vegetables that have a low nitrate content (below 500 mg/kg).

Nitrate itself poses only a very small, immediate health risk to adults. However, under certain circumstances (e.g., by bacteria in the mouth or stomach), nitrate can be partially converted into nitrite, which endangers human health: On the one hand, it can hinder the transport of oxygen in the blood in infants and thereby cause methemoglobinemia with blueness (cyanosis). On the other hand, nitrite can form so-called nitrosamines with secondary amines-these are nitrogen-containing chemical compounds that are found in many foods and medicines and are also formed during digestion.

Amines react with nitrous acid, which is present in sauerkraut, for example, to form different products depending on the type of amine used. Nitrosamines are chemical compounds that can form in the presence of substances such as nitrite and nitrogen oxides as well as certain secondary and tertiary amines. This is where they come from, among other things: In cured meat products, processed fish, beer and other alcoholic and non-alcoholic beverages. But they have also been detected in cheese, grains, processed vegetables, soy sauces and various oils. Most of these compounds have been shown to be carcinogenic in animal studies. Overall, the EFSA comes to the conclusion that dietary exposure to nitrosamines (P95; high consumption of foods containing nitrosamines), even taking into account the existing uncertainties, most likely indicates a health risk for all age groups [2].

The Central Nervous System (CNS): The Central Nervous System (CNS) includes parts of the nervous system that are surrounded by bones: The brain and the spinal cord. The brain lies entirely within the skull. The side view of the rat brain reveals three parts that are found in all mammals: The cerebrum, the cerebellum and the brainstem.

Early embryonic development: The CNS arises from the ectoderm. At the end of the 3rd week, the neural system consists of a slipper-shaped plate, the neural plate. The edges of the neural plate straighten up to form neural folds and form a small median depression, the neural groove. The caudal end is crossed by the primitive stripe and is divided into two elongated parts. The neural folds migrate towards each other and fuse in the midline (neurulation), whereby the neural groove becomes a tube, the neural tube. The latter differentiates further: The spinal cord arises from the caudal section, while the cranial part forms the primary cerebral vesicles. These represent the bases for the rhombencephalon, mesencephalon and prosencephalon. The embryonic brain vesicles are preserved in the course of complex brain development and form the cerebral ventricles in the adult.

Neural tube: The embryo is initially a flat disc with three separate layers of cells called the endoderm, mesoderm and ectoderm. The endoderm ultimately gives rise to the inner lining of many internal organs (“guts”, viscera). Skeletal bones and muscles develop from the mesoderm. The nervous system and skin eventually form entirely from the ectoderm. Our attention is focused on the changes in the part of the ectoderm from which the nervous system develops: The neural plate. At this early stage (in humans, about 17 days after fertilization), the brain consists of only a flat layer of cells. The next important event is the formation of a groove in the neural plate that runs in the rostral to caudal direction and is called the neural groove [3]. The walls of the groove are called neural ridges. They grow towards each other and fuse together on the dorsal side, forming the neural tube. The process by which the neural plate becomes the neural tube is called neurulation. Neurulation occurs very early in embryonic development, around 22 days after fertilization in humans. A common birth defect involves incomplete closure of the neural tube. Fortunately, research has recently shown that most defects of this type can be prevented by providing the mother with appropriate nutrition over the appropriate period of time. The formation of the neural tube is a crucial process in the development of the nervous system. It takes place in an early phase-just three weeks after fertilization-when the mother does not yet know anything about her pregnancy. A common birth defect involves incomplete closure of the neural tube. This affects approximately one in 500 live births. Recently, something of great public health importance has been discovered: Many neural tube defects are due to a deficiency of the vitamin folic acid in the mother's diet during the first weeks immediately after fertilization. According to one estimate, the occurrence of neural tube defects can be reduced by 90% if the diet is supplemented with folic acid during this period [4]. The formation of the neural tube is a complex process. The three-dimensional shape of individual cells must change in a precise sequence; the same applies to the adhesion between neighboring cells. In addition, the timing of neurulation must be coordinated with parallel changes in the non-neural ectoderm and the mesoderm. At the molecular level, successful neurulation depends on genes being expressed in a specific order, which is determined at least in part by the cell's location and local chemical environment. It is not surprising that this process is very sensitive to the presence or absence of chemical compounds in the maternal circulation.

Neural Tube Defect (NRD): The fusion of the neural crests, through which the neural tube forms, begins in the middle and continues anteriorly and posteriorly. If the anterior neural tube does not close, anencephaly occurs, a degeneration of the forebrain and skull that is always fatal. When the posterior neural tube fails to close, a condition called spina bifida occurs. The most severe form of this defect is

characterized by the neural plate not completely forming the lower spinal cord (bifida is the Latin term for a "two-part cleft"). Less severe forms are characterized by defects in the meninges and vertebrae overlying the posterior spinal cord. While spina bifida is not fatal, it requires intensive and expensive medical care. Folic acid is crucial in a number of metabolic pathways, such as the biosynthesis of DNA, which naturally occurs during development when cells divide. Although it is not yet clear exactly why folic acid deficiency leads to an increased occurrence of neural tube defects, it is easy to imagine how it disrupts the complex "choreography" of neurulation. The term "folic acid" is derived from the Latin word for "leaf". This is because folic acid was originally isolated from spinach leaves. In addition to green leafy vegetables, folic acid is also found in other foods such as liver, yeast, eggs, beans and oranges. Many breakfast cereals are now fortified with folic acid (Figure 1). Nevertheless, many people consume significantly less folic acid than is recommended for preventing birth defects (0.4 mg=day).

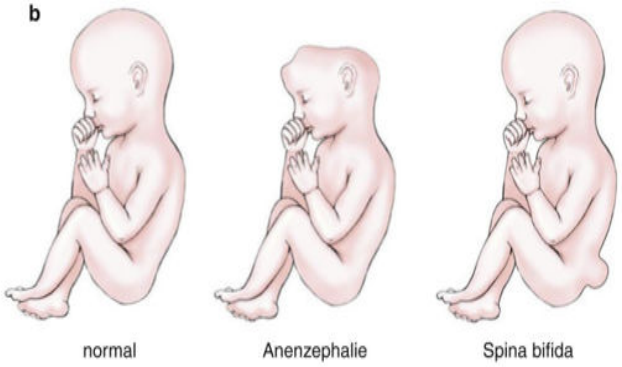

Figure 1. Neural tube defect.

Theoretical basis for the possible development of an arteriovenous malformation

Formaldehyde: Formaldehyde is produced industrially in large quantities and is contained in numerous (consumer-related) products. It also occurs in the cell metabolism of humans and other living beings. The substance is currently classified as "possibly carcinogenic" (K 3). In mid-2004, after an expert consultation, the International Agency for Research on Cancer (IARC) announced that, following a reassessment, formaldehyde would be considered a human carcinogen (sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans). The reason has not yet been published. (Toxicological assessment of formaldehyde-BfR statement no. 023/2006 dated March 30, 2006). In the case of formaldehyde, tumor development is based on two biological mechanisms of action that work together above a certain concentration: The cell-damaging effect, which triggers reactive cell proliferation, and the change in genetic information.

Irritant/cytotoxic effects of formaldehyde: In summary, the available evidence suggests that inhalation of formaldehyde poses a carcinogenic risk to humans at concentrations that are irritant or cytotoxic. At irritant/cytotoxic concentrations, inflammatory reactions and regenerative processes become crucial risk factors, formaldehyde-induced genotoxic events (DPX) are induced, DNA damage accumulates and malignant cell transformation is promoted. In the absence of cytotoxic effects and regenerative processes, the increase in tumor incidence due to formaldehyde exposure is practically negligible [5].

Lymphatic organs: The lymphatic organs can be roughly divided into the central or primary lymphatic organs, where the lymphocytes arise, and the peripheral or secondary lymphatic organs, in which mature naive lymphocytes are stabilized and adaptive immune responses are triggered. The central lymphoid organs are the bone marrow and the thymus (a large organ in the upper chest) (Figure 2).

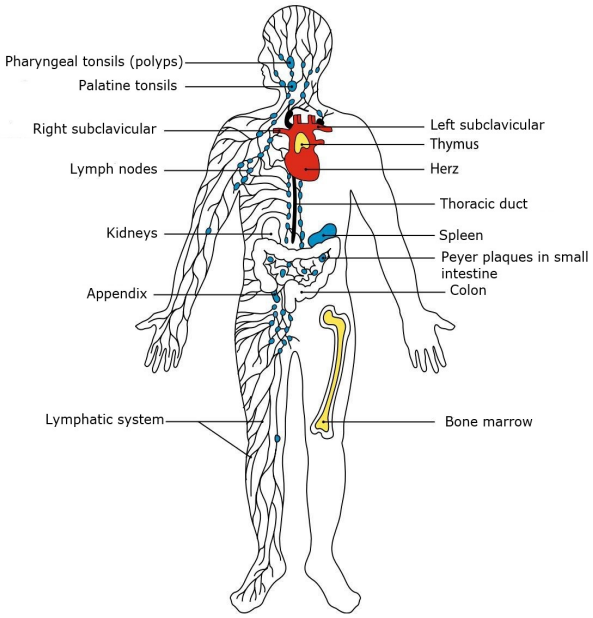

Figure 2. Lymphatic organs.

Lymphocytes: Lymphocytes circulate in the blood and lymphatic fluid, and they are found in large numbers in the lymphoid tissues or lymphoid organs. These are structured collections of lymphocytes in a network of non-lymphoid cells. Lymphocytes arise from stem cells in the bone marrow and differentiate in the central lymphoid organs (marked yellow in the image): B cells in the bone marrow and T cells in the thymus. From these tissues they reach the peripheral lymphatic organs (marked blue in the image) *via* the bloodstream: The lymph nodes, the spleen and the mucosa-associated lymphoid tissues (such as the gut-associated tonsils, Peyer's patches and the appendix). The peripheral lymphoid organs are the areas where the lymphocytes are activated by antigens. The lymphocytes circulate between the blood and these organs until they encounter an antigen. The lymphatic vessels direct the extracellular fluid from the peripheral tissues *via* the lymph nodes into the thoracic duct, which flows into the left subclavian vein (subclavian vein, subclavian vein). This fluid, called lymph, carries antigens taken up by dendritic cells and macrophages to the lymph nodes, and circulating lymphocytes from the lymph nodes back into the blood. Lymphoid tissues are also associated with other mucous membranes, such as the mucosal lining of the bronchi (not shown). The precursor cells that give rise to the B and T lymphocytes come from the bone marrow. B lymphocytes also mature there. The "B" of B lymphocytes originally stood for Bursa Fabricii, a

lymphatic organ in young chicks in which lymphocytes mature; but it can also stand for the English term bone marrow. The immature precursors of the T lymphocytes migrate to the thymus, after which they are also named, and mature there. After complete maturation, both types of lymphocytes enter the blood as mature naive lymphocytes. They circulate through the peripheral lymphoid tissues [6].

Thymus: The thymus, a general German term is not common, is the site of primary differentiation of T cells. From there they then migrate to the other lymphatic organs. The thymus arises primarily from the endoderm of the ventral diverticulum of the 3rd pharyngeal pouch. From there it grows caudally as a tube-like structure on both sides up to the pericardium. The thymus is surrounded by a connective tissue capsule. Below it is a single layer of epithelium made up of reticulum cells. This continues onto the incoming vessels and forms the blood-thymus barrier. It prevents contact with foreign antigens and thus enables the T lymphocytes to develop an unadulterated tolerance to the body's own antigen pattern. Inside the lobules, the epithelial reticulum cells arrange themselves into a network in whose meshes the lymphocytes lie. The thymus is divided into lobules, Lobuli thymici. In the periphery of the lobules, the lymphocytes are packed much more densely. This area is called the cortex. The precursors of the T cells reach the cortex *via* the subcapsular capillaries. Positive and negative selection take place here.

Involution: The thymus develops postnatally to a maximum development. This is achieved between the 8th week of life (hands, wdk.) and the end of the 1st year of life (horses). Then, usually earlier in the neck part, its regression (involution) begins. The thymus tissue is replaced by connective and fatty tissue. The proliferation of T lymphocytes occurs after the involution of the thymus in the T cell regions of the other lymphatic organs. However, it should be emphasized that the primary differentiation of T lymphocytes can only take place in the thymus. Removing the thymus before the T cells that have matured there are resettled means that a functional immune system cannot be built up [7].

Epithelium: Our body is protected on the surface by epithelia, which form a physical barrier between the internal area and the external world where pathogens reside. The epithelia include the skin and the lining of the tubular systems in the body, *i.e.* the respiratory, urogenital and gastrointestinal tracts. The epithelia in these areas are specialized for their particular functions and have their own innate defense mechanisms against the microorganisms to which they are normally exposed. The epithelial cells are held together by tight junctions, which form an effective barrier to the external environment. The inner epithelia are called mucosal epithelia because they release a viscous fluid (mucus, mucus). This contains numerous glycoproteins, the mucins. The mucus has a number of protective functions. Microorganisms that are covered with mucus can be prevented from attaching to an epithelium. The single-layer squamous epithelium consists of a layer of flat cells. Their cell body is often rolled out so thin that it can hardly be seen in histological sections. Only the cell nuclei can always be found if they lie in the section plane. Example: Epithelium of the pulmonary alveoli. Single-layered squamous epithelia, which form a lining of body cavities without connection to the outside world, have some special cell biological characteristics: Endothelium, the lining of blood vessels and heart cavities, is equipped with vimentin instead of cytokeratin filaments and VE-cadherin instead of E-cadherin and has no desmosomes (Figure 3).

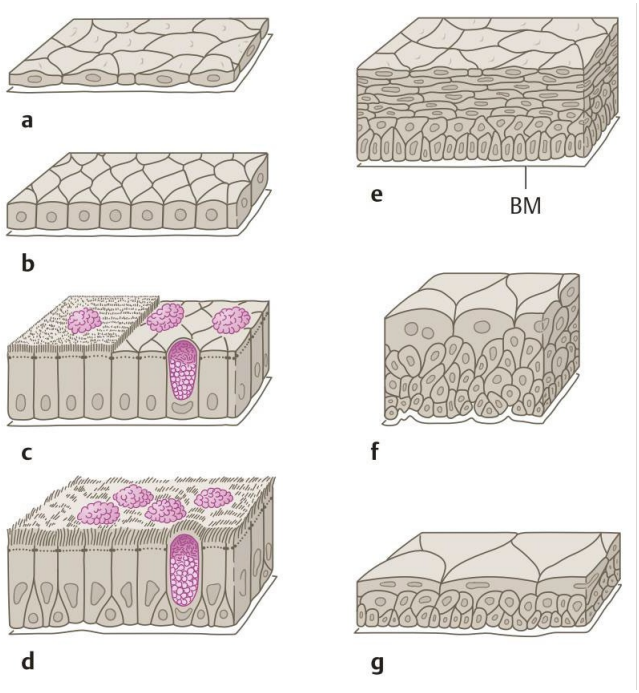

Figure 3. A) shows a single-layered squamous epithelium in comparison with non-layered cube; C) single layer cylindrical, with Burstensaum and Becherzelles; D) mehrreihig, with Kinozilien and Becherzellen; This multi-layered unhorned flat epithelium; F and G Urothel in the empty and filled bladder. BM=Basal Membrane.

Endothelium: The endothelium is a single-layer, gapless coating of flat, polygonal cells, which are aligned with their long axis parallel to the bloodstream and sit on a basal lamina. The ultrastructure of the endothelial cells in most sections of the vascular system corresponds to what is described for the continuous endothelium of the capillaries. The endothelial cells are connected to each other by adherens contacts, tight junctions and gap junctions (no desmosomes). The endothelium separates the intravascular space from deeper wall layers, controls the passage of plasma components and prevents contact between blood cells and the Extracellular Matrix (ECM). The apical surface is provided with a glycocalyx up to 500 nm thick (not visible in the usual preparation). The glycocalyx provides the endothelium with abundant negative charges, which is important for the selective permeability of the endothelium (e.g., glomerular capillaries). It also serves to bind and locally concentrate various molecules (e.g., antithrombotic substances, growth factors, cytokines, chemokines, enzymes), which overall influence intravascular events. The endothelial cells of the arteries form focal contacts with the ECM at their basal plasma membrane; on the cytosolic side of these contact points, insert contractile bundles of actin filaments that are oriented parallel to the direction of the blood flow (stress fibers). This

design allows the cells to withstand the strong shear forces that prevail here [8]. The adherens contacts between the endothelial cells are constructed similarly to those of the epithelia, but not with E-cadherin but with VE-cadherin (Vascular Endothelial cadherin) as a transmembrane protein. The durability of the adherens contacts is a prerequisite for the maintenance of the tight junctions and therefore has an indirect influence on the endothelial permeability.

Transendothelial exchange of substances in the capillary endothelium: The capillaries are the main site for gas and mass exchange. This is favored by the small layer thickness and the huge total surface area of the capillary endothelium as well as the slow flow of blood (approx. 0.5 mm/sec). Gases and substances with exclusively hydrophobic properties can diffuse through the endothelium without obstacles, following the concentration gradient. The following statements therefore concern the exchange of water and hydrophilic substances that cannot passively penetrate through membranes. Basically, two routes for passage are conceivable: (a) Transcellular route (through the endothelial cells, whereby these must have special passage points or transport mechanisms); (b) Paracellular pathway (between the endothelial cells, where the nature of the tight junctions is crucial). The degree of endothelial permeability varies so much depending on the organ that a general description is not possible. These differences are primarily due to the different structure of the endothelia. There are several basic types of endothelium. A basic type of endothelia is the fenestrated endothelium. This endothelium is equipped with the same cell contacts, vesicles, caveolae and a basal lamina as the continuous endothelium. In addition, it has sieve plate-like collections of windows (diameter 60–80 nm). Each window (exception see below) is provided with a diaphragm, the chemical composition of which has not yet been conclusively clarified. The only thing that is certain is that the windows have a lot of negative charges (probably because the long, negatively charged molecular chains of the glycocalyx cover the windows. The windows are places where water and small hydrophilic molecules can quickly pass through, plasma proteins because of their negative charge (and size) but hardly. Typical occurrence of fenestrated capillaries: e.g., endocrine organs, intestinal mucosa, peritubular capillaries of the kidney. The fenestrated endothelium has the same cell contacts, vesicles, caveolae and a basal lamina equipped like the continuous endothelium [9]. In addition, it has sieve-plate-like collections of windows (diameter 60-80 nm). Each window is provided with a diaphragm, the chemical composition of which has not yet been fully clarified. The only thing that is certain is that the windows with have many negative charges (probably because the long, negatively charged molecular chains of the glycocalyx cover the windows. The windows are places where water and small hydrophilic molecules can pass through quickly, but plasma proteins can hardly pass through because of their negative charge (and size). Typical occurrence of fenestrated capillaries: e.g., B. endocrine organs, intestinal mucosa, peritubular capillaries of the kidney. The fenestrated endothelium of the glomerular capillaries in the kidney occupies an intermediate position between “fenestrated” and “perforated”: The windows are of a similar size (70–100 nm) to those in the “truly” fenestrated endothelium, but do not have a diaphragm (“window without a windowpane”) and are therefore sometimes referred to as open pores. Purely descriptively they appear open, functionally they are probably just as little “open” as the fenestrae with diaphragm, because here as there the glycocalyx hangs over the pores and hinders the passage of anionic macromolecules. The endothelium sits on a very strong basal lamina, which is more similar to the fenestrated than to the perforated endothelium. The pore-like structure of Fenestrae and TEC is intended to enable a rapid exchange of molecules between the bloodstream and the tissue to be supplied. The fenestrated endothelium therefore has increased permeability to small and medium-sized molecules, which is why it plays an important role in the regulation of endocrine homeostasis. Accordingly, this endothelium is found in vascular beds of organs with increased filtration, secretion, or transendothelial transport. This applies, among other things, to exocrine and endocrine glands, the stomach and intestinal mucosa, the Choroid Plexus (PC), the renal glomeruli and part of the derrenal tubules (Figure 4).

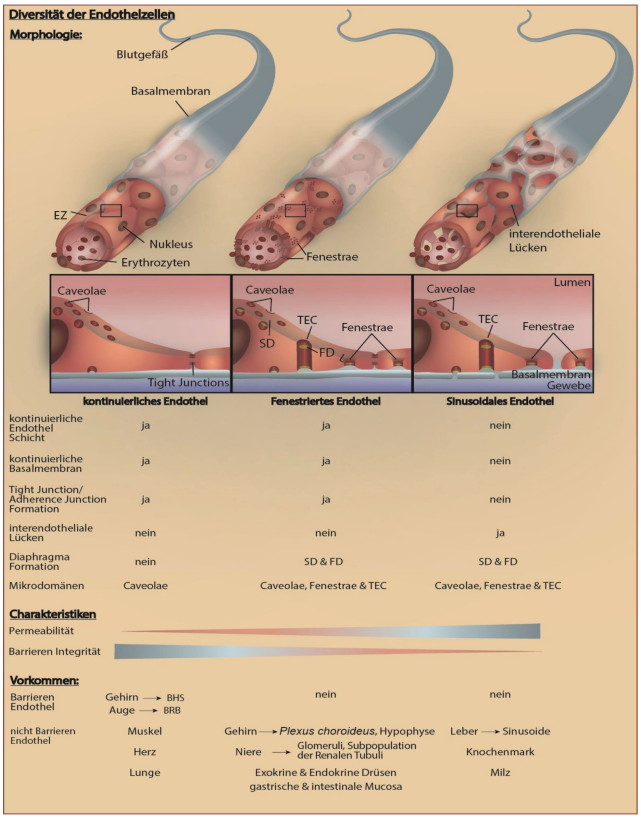

Figure 4. Schematic comparison of the three endothelial base types. This illustration presents the characteristics and similarities of continuous, fenestrated and sinusoidal endothelium with respect to their morphology (above), their characteristics and their origin (below).

Discussion

The circumventricular organs and neurohemal regions

The neurohemal regions are narrowly defined areas of the brain in which a blood-specific environment prevails, as there is no blood-brain barrier here. The capillaries have fenestrated endothelium and are surrounded by wide perivascular spaces. The diffusion of hydrophilic molecules from the blood to the extracellular space (ECR) of the brain and vice versa is not hindered. The neurohemal regions include the median eminence in the infundibulum of the neurohypophysis, the posterior pituitary gland, the area postrema in the wall of the fourth ventricle and some areas in the wall of the third ventricle. The functional significance of this construction is known in some cases: Passage of neurohormones released from axonal boutons into the blood (eminentia mediana, posterior pituitary gland); access for hydrophilic substances that circulate in the blood to the neurons (area postrema: "trigger zone" for the vomiting reflex, e.g., in the event of poisoning). The absence of the blood-brain barrier requires a barrier between the ECR of the neurohemal regions and the CSF. This barrier is formed by a special ependyma that is poor in kinocilia and has tight junctions. In some regions (e.g., eminentia mediana, see above) these are slender, elongated cells called tanycytes. Because of their topographical location, the neurohemal regions are also referred to as circumventricular organs.

Blood-brain barrier

The barrier with the largest surface between the blood circulation and the Central Nervous System (CNS) is the Blood-Brain Barrier (BBB). It is formed from the EZ that forms the capillaries, which are separated by the Tight Junction (TJ) proteins Zonula Occludens 1-3 (ZO1-3) and Adherens Junctions (AJ) proteins like cadherins are tightly connected to each other. The cell-cell connections formed are often multi-row, creating a physical barrier that is impassable for many molecules. This effect is reinforced by the absence of fenestrations, as occur in other endothelia, and a very small number of pinocytic vesicles. To maintain the BBB and its functionality, astrocytes and pericytes are also connected to the EC, with pericytes and ECs forming a particularly close connection with one another. This creates the so-called basal lamina, which is surrounded by the end feet of the astrocytes in the space of the extracellular matrix. Other cell types of the extracellular matrix, such as microglia and the endings of nerve cells, also contribute to the support of the BBB. However, the endothelial cell layer of the BBB also represents a connection between the CNS and the peripheral circulation and, despite the greatly reduced paracellular and transcellular transport compared to other capillary endothelia, must supply the underlying tissue with sufficient nutrients [10]. The most important transport systems include receptor-mediated endocytosis, active efflux transport by solute carrier transporters and ion transport. Therefore, the BBB has a number of specialized Adenosine Triphosphate (ATP)-Binding Cassette (ABC) transporters and other transcytosis mechanisms that regulate the influx of macromolecules and thus the exchange of substances between the blood and the CNS. Together they represent the chemical component of the barrier that enables selective exchange. The large number of mitochondria in the EC of the BBB, which have to cover their energy requirements and metabolic activity, support the selective exchange by different selective transporters (Figure 5).

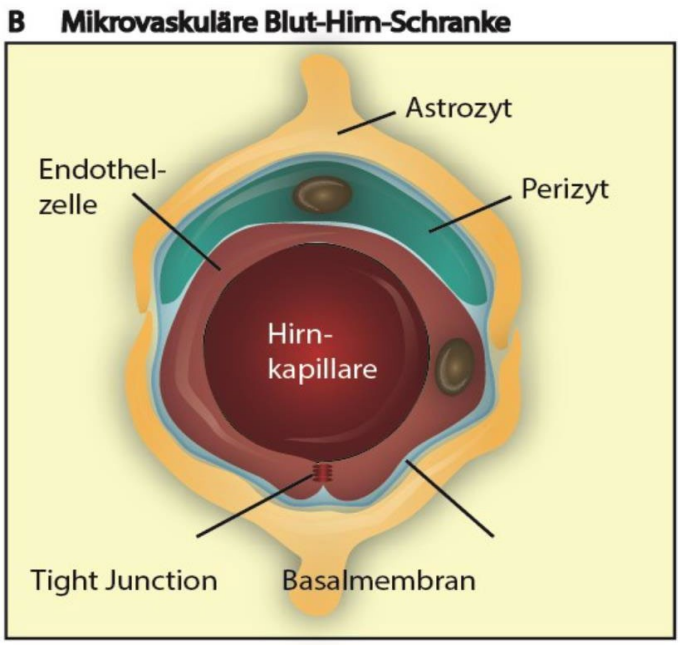

Figure 5. Construction of a fenestrated endothelial cell (EZ) within the blood-brain barrier.

Lymphoepithelial organ

A lymphoepithelial organ is an organ of the lymphatic system whose framework is formed by an epithelium. The lymphoepithelial organs include the tonsils of the Waldeyer pharyngeal ring (tonsilla pharyngea, tonsilla palatina, tonsilla lingualis, tonsilla tubaria), the thymus and the bursa of Fabricii. In the other lymphatic organs, however, the basic structure is formed by a reticular connective tissue (lymphoreticular organ). In the tonsils, lymphatic tissue accumulates directly beneath the depressions (crypts) of the epithelium. With the transfer of lymphocytes (leukodiapedesis), the epithelium loosens, which, in the case of massive diapedesis, almost takes on a reticular appearance ("dedifferentiation"). The thymus differs from the other lymphoepithelial organs in that the endoderm epithelium of the branchial intestine detaches and shifts during organogenesis. The epithelium dissolves and an "epithelial reticulum" is created. The thymus also has an organ capsule (Table 2).

	Organ	Epithel	Drusen	Lymphfollicle	Features
Lympho-epithelial organs	Tonsilla lingualis	Multilayered stratified epithelium	Mukose Drusen (for Crypten)	+	Lung tissue, no capsule
	Tonsilla palatina	Multilayered stratified epithelium	Mucose Drusen (Not for Crypten)	+	Kapsuläre separation
	Tonsilla pharyngea	Mehrreihiges cylindricalepithelial	Seromukose Drusen (for Crypten)	+	Irregular Heteromorphic surface, Epithel
	Thymus	(Epithelial reticulum)	o	None	Lappchen-gliderung, Hassalsche Karchen
Lympho-reticular organs	Lymph nodes	o	o	+ (nur Rinde)	Rind and Mark, Randsinus, Lymph vessels
	Milz	o	o	+ (ubiquitous, with central artery)	Muscular capsule Red pulp, Trabekelnetz

Table 2. Differential diagnosis of lymphatic organs.

Diapedesis: Diapedesis refers to the migration of blood cells through the vessel walls into the tissue. Lymphocytes enter the lymph nodes at different stages. The lymphocytes first roll along the endothelial surface, then the integrins are activated, the adhesion strengthens and diapedesis follows, *i.e.* the penetration of the endothelial layer into the paracortical zones, the T cell zones (Figure 6).

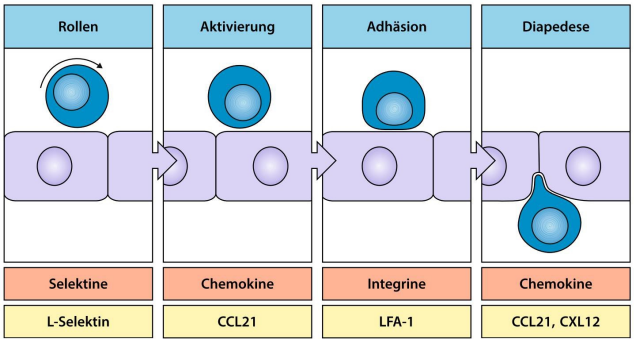

Figure 6. Diapedesis.

Necrosis and erythrodiapedesis: Morphologically, two fundamentally different forms of cell death can be distinguished: Necrosis and apoptosis (shrinkage necrosis). Necrosis occurs as a result of damage that exceeds the cell's adaptive capacity. It is defined as the sum of all morphological phenomena after (provoked) cell or tissue death. Tissue destruction that is accompanied by severe bleeding is called hemorrhagic necrosis [11]. As part of the organism's inflammatory reaction, supported by pathogen toxins, the walls of the capillaries and venules are damaged to such an extent that the erythocytes can escape into the tissue (erythrodiapedesis). Influenza tracheitis and pneumonia typically progresses with the appearance of a hemorrhagic nectrosing inflammation. The organism's reaction is triggered by the nectrosis itself. Phospholipase activation in the necrotic cells results in the release of arachidonic acid derivatives (prostaglandins, leukotrienes), which attract granulocytes and macrophages (necrotaxis). In addition, these substances have a vasoactive effect and lead to blood circulation in the surrounding area [12]. Immigrated macrophages, blood platelets, endothelial cells, smooth muscle cells, vascular endothelia and fibroblasts release numerous growth and angiogenesis factors that induce fibroblast life and new capillary formation. Important growth factors are FGF (Fibroblast Growth Factor), PDGF (Platelet-Derived Growth Factor), TGF-ß (Transforming Growth Factor-ß) and the Vascular Endothelial Growth Factor (VEGF).

Interpretation

A congenital arteriovenous fistula in adolescence: With regard to these extensive theoretical principles, a congenital arteriovenous fistula arises from a split in the spine (spina bifida). This is a neural ear malformation. The neural ear is formed during embryonic development in the womb. A SEP measurement by Mr. F. Maier (arteriovenous malformation patient) from August 2nd, 2023 underlines this theory (pathological side difference) (Figure 7-9).

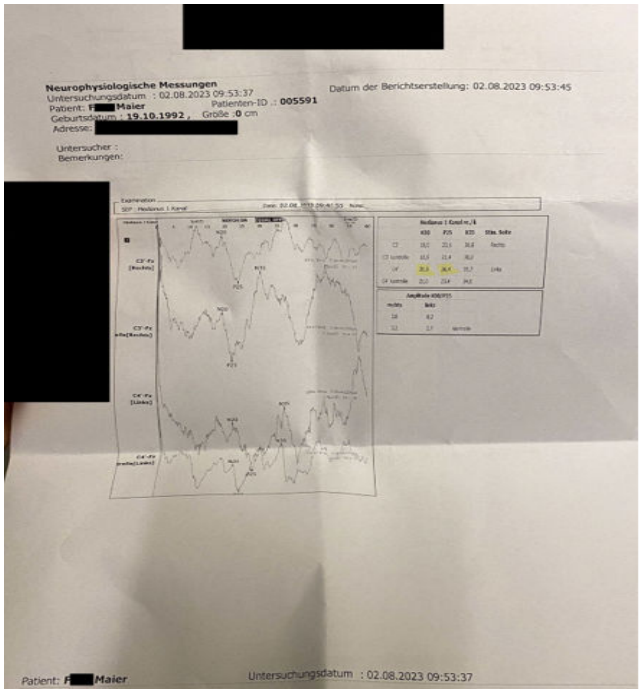

Figure 7. A SEP measurement by Mr. F. Maier.

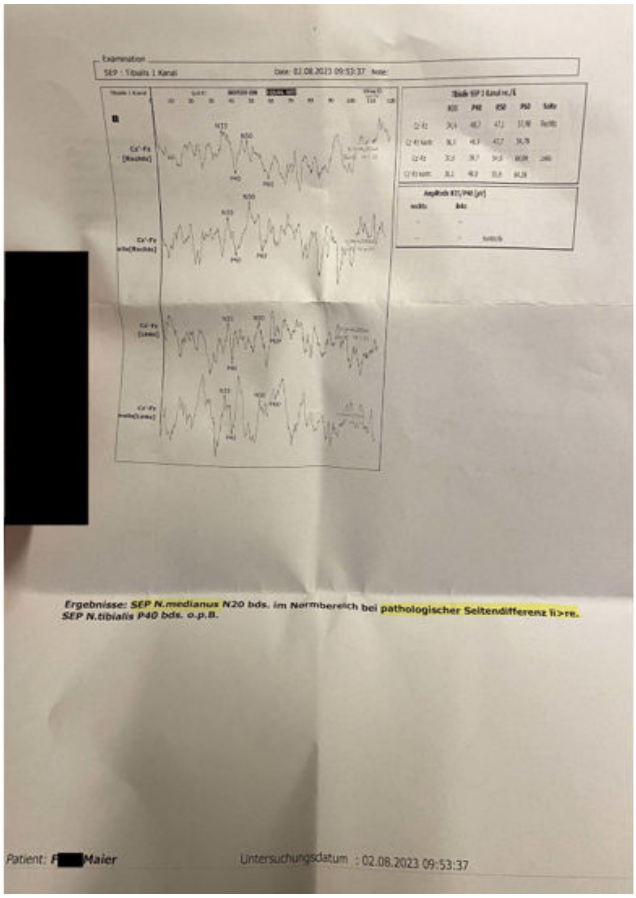

Figure 8. A SEP measurement by Mr. F. Maier (arteriovenous malformation patient) from August 2nd, 2023.

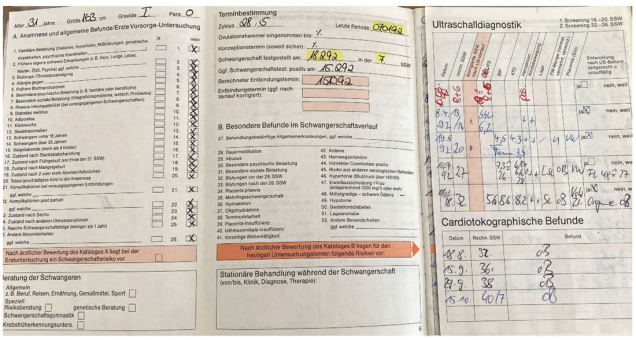

Figure 9. The patients SEP measurements.

Ms. B. Maier (née Peters) stated that after discovering her pregnancy on February 18, 1992, she had eaten a large portion of sauerkraut. The pregnancy was confirmed in the 7th week of pregnancy. (Although I count 42 days-6th week of pregnancy from the last period on January 7th, 1992 until the pregnancy was confirmed on February 18th, 1992. In the 6th week of pregnancy, the end of the spinal cord is formed in the phoetus).

An arteriovenous malformation in adolescence

A congenital arteriovenous fistula can only mutate into an arteriovenous malformation because an important developmental step in the generation of cytotoxic T cells (lymphocytes) does not take place in all lymphoepithelial organs, occurs incorrectly or only slightly, organs, occurs incorrectly or only slightly, thus allowing cytotoxic cells to overcome the blood-thymus barrier. The development step of the cytotoxic T cells in the thymus ensures that the cells are able to recognize foreign antigens and to ignore the body's own antigens. The thymus is a lymphoepithelial organ whose framework is formed by an epithelium. In arteriovenous malformation patients, the epithelium is damaged in the fetus (see gravidogram by B. Maier on the next page) or is inherited due to familial predisposition. The cytotoxicity of formaldehyde damages the vessel walls of the circumventricular organs because there is no blood-brain barrier there and the cytotoxic cells are therefore not stopped. The permeable fenestrated endothelial layer consists of capillaries. Since there are no capillaries in congenital arteriovenous fistulas, but a permeable fenestrated endothelial layer, diapedesis occurs when severe blood congestion occurs. This form of cell penetration is called erythrodiapedesis. Erythodiapedesis can therefore lead to a mutagenic cell transformation, which causes a nidus of small vessels, an arteriovenous malformation, to form around the congenital arteriovenous fistula (Figure 9).

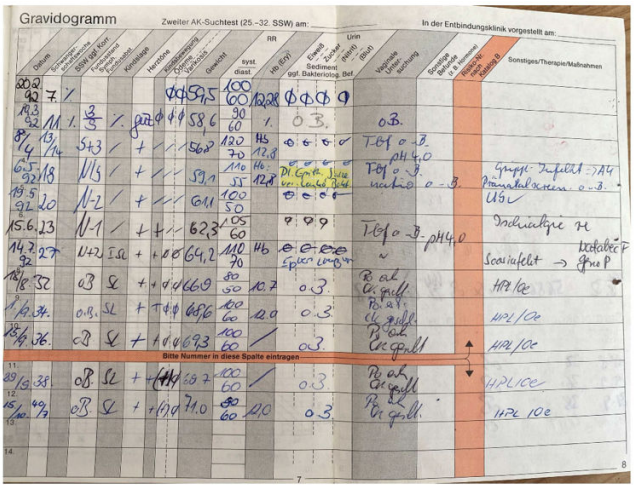

Figure 10. From the gravidogram from May 6, 1992 I can see the abbreviation DI. Epith. Salts ver. Leuko Bact. ...decipher. In my interpretation, this could be an abbreviation for “bacterial salts” in the epithelium, decreased leukocytes.

A congenital arteriovenous fistula in a newly grown adult

A congenital arteriovenous fistula is congenital and can only be eliminated with existing therapeutic measures such as angiography with embolization or radiation. I question the usefulness of this approach because a new congenital arteriovenous fistula is formed by the body after a certain period of time.

An arteriovenous malformation in overgrown alter

When transferring/changing from the formation of lymphocytes in the thymus to the lymphatic organs, e.g., B. Paracortex in the lymph node, PALS in the spleen), the lymphocytes are no longer formed by a lymphoepithelial organ, but by a lymphoreticular organ. The stroma (the supporting, loose connective tissue) does not consist of very thin squamous epithelia (endothelium), but of reticular connective tissue (reticulum cells, whose processes form a wide-meshed network in

which reticulin fibers (type 3 collagen) are embedded. The reticulin fibers are formed by the reticulum cells and strengthen the tissue. Due to this change, no arteriovenous malformation can arise in adulthood or a new nidus around a congenital arteriovenous fistula. Nevertheless, an arteriovenous malformation can have arisen in adolescence and only break out in adulthood. Speculative the toxic amino acid homocysteine is responsible for the pulse-synchronous throbbing resulting from the outbreak of arteriovenous malformation and arteriovenous fistula in adulthood. Folic acid is involved in a large number of metabolic processes and is therefore important for all cell division and growth processes. (Folic acid BfR 2023) Folate is mainly active inside the cells. For example, the vitamin is involved in the formation of genetic material (DNA) and thus in cell division and all growth and healing processes. A massive folate deficiency can lead to very different symptoms, such as: B. Hair loss, skin problems, depressive moods, anemia (anemia) and a regression of the mucous membranes with subsequent inflammation of the mucous membranes in the gastrointestinal tract (stomach problems, diarrhea, inflammation of the oral mucosa, etc.) or in the urogenital tract (urinary tract, vagina, bladder). In pregnant women, a folate deficiency is said to increase the rate of premature births and miscarriages and lead to neural tube defects ("open back") in infants. However, what is probably responsible for the prevention of a stroke (and possibly a heart attack) is the ability of vitamin B_9, together with vitamins B_6 and B_{12}, to break down the toxic amino acid homocysteine. Since the AVM patient (F. Maier) took folic acid as a dietary supplement for 3 months, he no longer notices pulse-synchronous throbbing. 1st month folic acid intake twice a week with vitamin B_6 and B_{12} 500 mg, 2nd and 3rd month folic acid intake once a week with vitamin B_6 and B_{12} 500 mg. Current folic acid intake based on feeling.

Conclusion

Arteriovenous Malformation (AVM) is a vascular anomaly that can lead to serious complications, such as hemorrhage or neurological symptoms. While AVMs are not infectious, clusters of cases in a specific area may be misinterpreted as an outbreak, especially if there is a series of hemorrhagic events or similar neurological symptoms. Misdiagnosis could delay appropriate treatment, making AVM a potential cause of confusion in outbreak investigations. However, AVMs are congenital or developmental conditions, not infectious, and their occurrence in clusters requires careful diagnostic assessment to distinguish them from true outbreaks.

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