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Rare Juvenile Primary Systemic Vasculitis

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1. WHAT IS VASCULITIS

1.1 What is it?

Vasculitis is inflammation of the blood vessel walls. Vasculitides include a wide group of diseases. The term "primary" means that the blood vessel is a major disease target with no other underlying disease. The classification of vasculitides depends mainly on the size and type of blood vessels involved. There are many forms of vasculitis, ranging from mild to potentially life-threatening. The term "rare" refers to the fact that this group of diseases is very uncommon in childhood.

1.2 How common is it?

Some of the acute primary vasculitides are quite common paediatric diseases (e.g. Henoch-Schönlein purpura and Kawasaki disease), while the others described below are rare and their exact frequency is unknown. Sometimes, parents have never heard the term "vasculitis" before the child is diagnosed. Henoch-Schönlein purpura and Kawasaki disease are covered in their own sections.

1.3 What are the causes of the disease? Is it inherited? Is it infectious? Can it be prevented?

Primary vasculitides do not usually run in the family. In the majority of cases, the patient is the only one affected in a family and it is very unlikely that siblings get the same disease. It is most likely that a combination of different factors plays a part in causing the disease. It is believed that various genes, infections (acting as triggers) and

environmental factors may be important for the disease development. One exception is a very recently described form of vasculitis, called "DADA2", but this is very rare.
These diseases are not infectious and cannot be prevented or cured, but they be controlled - meaning the disease is not active and its signs and symptoms go away. This state is called "remission".

1.4 What happens to the blood vessel in vasculitis?

The blood vessel wall is attacked by the body's immune system, causing it to swell and resulting in structural disruption. Blood flow is impaired and blood clots may form in the inflamed vessels. Together with the swelling of the vascular walls, this effect may contribute to vessel narrowing or occlusion.
The inflammatory cells from the blood stream gather in the vessel wall, causing more damage to the vessel and to the surrounding tissue as well. This can be seen in tissue biopsy samples.
The vessel wall itself becomes more "leaky", allowing the fluid from within the blood vessels to enter the surrounding tissues and causing swelling. These effects are both responsible for the various types of rashes and skin changes seen in this group of diseases.
Decreased blood supply through narrowed or blocked vessels or, less frequently, vessel wall rupture with bleeding, may damage the tissues. Involvement of the vessels supplying vital organs like the brain, kidneys, lungs or heart can be a very serious condition. Widespread (systemic) vasculitis is usually accompanied by extensive release of inflammatory molecules, causing general symptoms like fever, malaise, as well as abnormal laboratory tests detecting inflammation: erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP). The abnormalities of the vessel shape in the larger arteries can be detected through angiography (a radiological investigation procedure that allows us to see the blood vessels).

2. DIAGNOSIS AND THERAPY

2.1 What are the types of vasculitis? How is vasculitis classified?

Vasculitis classification in children is based on the size of the blood

vessel involved. Large vessel vasculitis, like Takayasu arteritis, affects the aorta and its major branches. Medium vessel vasculitis typically affects arteries supplying the kidneys, bowels, brain or heart (e.g. polyarteritis nodosa, Kawasaki disease). Small vessel disease involves smaller blood vessels including capillaries (e.g. Henoch-Schönlein purpura, granulomatosis with polyangiitis or GPA, eosinophilic granulomatosis with polyangiitis or EGPA, previously referred to as Churg-Strauss syndrome), cutaneous leukocytoclastic vasculitis, microscopic polyangiitis).

2.2 What are the main symptoms?

Disease symptoms vary according to the overall number of inflamed blood vessels (widespread or just a few sites) and their location (vital organs like brain or heart versus skin or muscle) as well as the degree of blood supply compromise. This can vary from a transient minor decrease of blood flow to complete occlusion with subsequent changes to the unsupplied tissue caused by the lack of oxygen and nutrient supply. This can eventually lead to tissue damage with subsequent scarring. The extent of tissue damage indicates the degree of tissue or organ dysfunction. Typical symptoms are described under the individual disease sections below.

2.3 How is it diagnosed?

Diagnosis of vasculitis can be challenging. The symptoms resemble other various, more common paediatric illnesses. The diagnosis is based on an expert evaluation of clinical symptoms, together with the results of blood and urine tests and imaging studies (e.g. ultrasonography, X-rays, CT and MRI scans, angiography). Where appropriate, diagnosis is confirmed by biopsies taken from the involved and most accessible tissues or organs. Because it is rare, it is often necessary to refer the child to a centre where paediatric rheumatology is available, as well as other paediatric subspecialties and imaging experts.

2.4 Can it be treated?

Yes, today vasculitis can be treated, although some more complicated

cases offer a real challenge. In the majority of properly treated patients, disease control (remission) can be achieved.

2.5 What are the treatments?

The treatment for primary chronic vasculitis is long-term and complex. Its main goal is to get the disease under control as soon as possible (induction therapy) and to maintain the control long-term (maintenance therapy), while avoiding drug side effects where possible. Treatments are chosen on a strictly individual basis according to the patient´s age and the disease severity.

In combination with immunosuppressive drugs, such as cyclophosphamide, and corticosteroids have proven to be most effective in inducing disease remission.

Drugs regularly used in maintenance therapy include: azathioprine, methotrexate, mycophenolate mofetil and low-dose prednisone. Various other drugs can be used to suppress the activated immune system and fight inflammation. They are chosen on strictly individual basis, usually when other common drugs have failed. They include the newest biological agents (e.g. TNF inhibitors and rituximab), colchicine and (less commonly) thalidomide.

For any patient requiring long-term corticosteroid therapy, osteoporosis should be prevented by sufficient calcium and vitamin D intake. Drugs that affect blood clotting may be prescribed (e.g. low-dose aspirin and/or anticoagulants) and, in the event of raised blood pressure, blood pressure lowering agents are used.

Physiotherapy may be needed to improve musculoskeletal function, while psychological and social support for the patient and the family helps them to cope with the stress and strains of a chronic disease.

2.6 What about unconventional/complementary therapies?

There are many complementary and alternative therapies available and this can be confusing for patients and their families. Think carefully about the risks and benefits of trying these therapies as there is little proven benefit and they can be costly both in terms of time, burden to the child and money. If you want to explore complementary and alternative therapies, it is wise to discuss these options with your paediatric rheumatologist. Some therapies can adversely interact with

conventional medications. Most doctors will not be opposed to complementary therapies, provided you follow medical advice. It is very important not to stop taking your prescribed medications. When medications such as corticosteroids are needed to keep the disease under control, it can be very dangerous to stop taking them if the disease is still active. Please discuss medication concerns with your child’s doctor.

2.7 Check-ups

The main purpose of regular follow-up is to evaluate the activity of the disease and the efficacy and possible side effects of the treatment, in order to achieve maximum benefit for your child. The frequency and type of follow-up visits depend on the type and severity of the disease, as well as on the drugs used. In the early stage of the disease, outpatient visits are typical and, in more complicated cases, inpatient admissions can be more frequent. These visits usually become less frequent as soon as disease control is achieved.
There are several ways to evaluate disease activity in vasculitis. You will be asked to report any changes in your child’s condition and in some cases to follow his/her urine dip-stick tests or blood pressure measurements. Detailed clinical examination together with the analysis of your child’s complaints form an important part of the evaluation of disease activity. Blood and urine tests are performed to detect activity of inflammation, changes in organ functions and potential drug side effects. Based on individual internal organ involvement, various other investigations might be performed by different specialists and imaging studies may be required.

2.8 How long will the disease last?

Rare primary vasculitides are long-term, sometimes life-long diseases. They can start as an acute, often severe or even life-threatening condition, and subsequently evolve into a more chronic low-grade disease.

2.9 What is the long-term evolution (prognosis) of the disease?

Prognosis of rare primary vasculitides is highly individual. It depends not only on the type and extent of vessel involvement and the organ involved, but also on the interval between disease onset and the start of treatment as well as on the individual response to therapy. The risk of organ damage is related to the duration of active disease. Damage to the vital organs can have life-long consequences. With proper treatment, clinical remission is often achieved within the first 6-12 months. The remission can be life-long but long-term maintenance therapy is often needed. Periods of disease remission may be interrupted by disease relapses requiring more intensive therapy. Untreated disease has relatively high risk of death. Because the disease is rare, exact data on long-term disease evolution and mortality are scarce.

3. EVERYDAY LIFE

3.1 How might the disease affect the child and the family's daily life?

The initial period, when the child is unwell and the diagnosis is yet to be made, is usually very stressful for the whole family.
Understanding the disease and its therapy helps the parents and the child to cope with often unpleasant diagnostic and therapeutic procedures and frequent hospital visits. Once the disease is under control, home and school life can usually return to normal.

3.2 What about school?

Once the disease is reasonably controlled, patients are encouraged to go back to school as soon as they can. It is important to inform the school about the child´s condition so that it can be taken into account.

3.3 What about sports?

Children are encouraged to take part in their favourite sport activities once disease remission is achieved.
Recommendations might vary according to the possible presence of organ functional impairment, including muscles, joints and bone status, which may be influenced by previous corticosteroid use.

3.4 What about diet?

There is no evidence that a special diet can influence the disease course and outcome. A healthy, well-balanced diet with sufficient protein, calcium and vitamins is recommended for a growing child. While a patient is receiving corticosteroid treatment, sweet, fat or salty food intake should be limited in order to minimise the side effects of corticosteroids.

3.5 Can climate influence the course of the disease?

Climate is not known to influence the course of the disease. In the event of impaired circulation, mainly in cases of vasculitis of the fingers and toes, exposure to cold can make the symptoms worse.

3.6 What about infections and vaccinations?

Some infections may have a more serious outcome in individuals treated with immunosuppressive drugs. In case of contact with chickenpox or shingles, you should contact your physician immediately in order to receive an anti-virus drug and/or specific anti-virus immunoglobulin. The risk of ordinary infections may be slightly higher in treated children. They may also develop unusual infections with agents that do not affect individuals with fully functional immune system. Antibiotics (co-trimoxazol) are sometimes administered long-term to prevent lung infection with a bacteria called Pneumocystis, which can be a life-threatening complication in immunosuppressed patients. Live vaccines (e.g. mumps, measles, rubella, polios, tuberculosis) should be postponed in patients receiving immunosuppressive treatments.

3.7 What about sexual life, pregnancy, birth control?

In sexually active adolescents, birth control is important as the majority of drugs used may damage the developing foetus. There are concerns that some cytotoxic drugs (mainly cyclophosphamide) might affect a patient’s ability to have a child (fertility). This depends mainly on the total (cumulative) dose of the drug received over the period of

treatment and is less relevant when the drug is administered in children or pre-pubertal adolescents.

4. POLYARTERITIS NODOSA

4.1 What is it?

Polyarteritis nodosa (PAN) is a form of vessel wall-destroying (necrotising) vasculitis affecting mainly medium and small arteries. The vessel walls of many ("poly") arteries - polyarteritis - are affected in a patchy distribution. Inflamed parts of the artery wall become weaker and under the pressure of the blood stream, small nodular outpouchings (aneurysms) form along the artery. This is the origin of the name "nodosa". Cutaneous (skin) polyarteritis affects predominantly skin and musculoskeletal tissue (sometimes also muscles and joints) and not the internal organs.

4.2 How common is it?

PAN is very rare in children, with an estimated number of new cases per year of one per million. It affects boys and girls equally and is more commonly seen in children around 9-11 years of age. In children, it may be associated with streptococcal infection or much less frequently also with hepatitis B or C. Recently, a genetic form of PAN has been described called DADA2. The gene can be tested for in (very few) specialist centres, and is not always routinely available currently.

4.3 What are the main symptoms?

The most common general (constitutional) symptoms are prolonged fever, malaise, fatigue and weight loss.
The variety of localised symptoms depends on the organs affected. Insufficient blood supply to the tissue causes pain. Therefore, pain at various sites may be a leading symptom of PAN. In children, muscle and joint pain is as frequent as abdominal pain, which is due to the involvement of gut-supplying arteries. If the vessels supplying the testes are affected, scrotal pain may also occur. Skin disease can present as a wide range of changes from painless rashes of various appearance (e.g. spotty rash called purpura or purplish skin mottling

called livedo reticularis) to painful skin nodules and even ulcers or gangrene (complete loss of blood supply causing damage to peripheral sites including fingers, toes, ears or the tip of the nose). Kidney involvement can result in the presence of blood and protein in urine and/or raised blood pressure (hypertension). The nervous system can also be affected to a variable degree and the child may have seizures, stroke or other neurological changes.
In some severe cases, the condition can worsen very quickly.
Laboratory tests usually show marked signs of inflammation in the blood, with high white blood cell counts (leukocytosis) and a low level of haemoglobin (anaemia).

4.4 How is it diagnosed?

To consider a diagnosis of PAN, other potential causes of persistent fever in childhood should be excluded, such as infections. The diagnosis is then supported by the persistence of systemic and localised manifestations despite antimicrobial treatment, which is usually administered to children with persistent fever. The diagnosis is confirmed by the demonstration of vessel changes through imaging (angiography) or by the presence of vessel wall inflammation in a tissue biopsy.
Angiography is a radiological method where blood vessels that are not seen on ordinary X-rays are visualised by contrast fluid that has been injected directly into the blood stream. This method is known as conventional angiography. Computed tomography can also be used (CT angiography).

4.5 What is the treatment?

Corticosteroids remain the mainstay of treatment for childhood PAN. The mode of administration for these drugs (often directly into veins when the disease is very active, later in tablets) and the dose and duration of treatment are tailored individually according to a careful assessment of disease extent and severity. When the disease is limited to the skin and musculoskeletal system, other drugs suppressing immune functions may not be necessary. However, severe disease and vital organ involvement requires early addition of other medication, usually cyclophosphamide, in order to achieve disease control (so-called

induction therapy). In cases with severe and unresponsive disease, other drugs including biologic agents are sometimes used but their efficacy in PAN has not been formally studied.
Once disease activity settles, it is kept under control with maintenance therapy, usually with azathioprine, methotrexate or mycophenolate mophetil.
Additional treatments used on an individual basis include penicillin (in case of post-streptococcal disease), drugs that dilate blood vessels (vasodilators), blood pressure lowering agents, drugs against blood clot formation (aspirin or anticoagulants), painkillers (non-steroidal anti-inflammatory drugs, NSAIDs).

5. TAKAYASU ARTERITIS

5.1 What is it?

Takayasu arteritis (TA) affects mainly large arteries, predominantly the aorta and its branches and the main lung (pulmonary) artery branches. Sometimes the terms "granulomatous" or "large-cell" vasculitis are used, referring to the main microscopic feature of small nodular lesions formed around a special type of large cell ("giant cell") in the artery wall. In some lay literature, it is also referred to as the ‘pulseless disease’, since in some cases the pulses in the extremities may be absent or unequal.

5.2 How common is it?

Worldwide, TA is considered relatively frequent due to its more common occurrence in the non-white (mainly Asian) population. It is very rare in Europeans. Girls (usually during adolescence) are affected more frequently than boys.

5.3 What are the main symptoms?

Early disease symptoms include fevers, loss of appetite, weight loss, muscle and joint pain, headache and night sweats. Laboratory markers of inflammation are increased. As the artery inflammation progresses, signs of diminished blood supply are apparent. Increased blood pressure (hypertension) is a very frequent initial symptom in childhood

disease due to the involvement of abdominal arteries affecting blood supply to the kidneys. Loss of peripheral limb pulses, differences in blood pressure in different limbs, murmurs heard with the stethoscope over the narrowed arteries and sharp extremity pain (claudication) are common signs. Headaches, various neurological and eye symptoms may be a consequence of the disturbed blood supply to the brain.

5.4 How is it diagnosed?

Ultrasound examination using the Doppler method (for blood flow assessment) is useful as a screening or follow-up method to detect involvement of major arterial trunks close to the heart, although this method often fails to detect involvement of more peripheral arteries. Magnetic resonance (MR) imaging of blood vessel structure and blood flow (MR angiography, MRA) is the most appropriate method for visualising large arteries such as the aorta and its main branches. In order to see smaller blood vessels, X-ray imaging may be used, where blood vessels are visualised by contrast fluid (which is injected directly into the blood stream). This is known as conventional angiography. Computed tomography can be used as well (CT angiography). Nuclear medicine offers an examination called PET (Positron Emission Tomography). A radioisotope is injected into the vein and recorded by a scanner. Accumulation of the radioisotope at actively inflamed sites demonstrates the extent of arterial wall involvement.

5.5 What is the treatment?

Corticosteroids remain the mainstay of the treatment for childhood TA. Their mode of administration and the dose and duration of treatment are tailored individually according to careful assessment of disease extent and severity. Other agents suppressing immune functions are often used early in the disease course in order to minimize the need for corticosteroids. Frequently used drugs include azathioprine, methotrexate or mycophenolate mophetil. In cases of severe disease, cyclophosphamide is used first in order to achieve disease control (so-called induction therapy). In cases with severe, unresponsive disease, other drugs including biologic agents (such as TNF blockers or tocilizumab) are sometimes used but their efficacy in childhood TA has not been formally studied.

Additional treatments used on an individual basis include drugs that dilate blood vessels (vasodilators), blood pressure lowering agents, drugs against blood clot formation (aspirin or anticoagulants) and painkillers (non-steroidal anti-inflammatory drugs, NSAIDs).

6. ANCA-ASSOCIATED VASCULITIS: Granulomatosis with polyangiitis (Wegener`s, GPA) and Microscopic polyangiitis (MPA)

6.1 What is it?

GPA (previously called Wegener's granulomatosis) is a chronic systemic vasculitis affecting mainly the small blood vessels and tissues in the upper airways (nose and sinuses), lower airways (lungs) and kidneys. The term "granulomatosis" refers to the microscopic appearance of the inflammatory lesions that form small multi-layered nodules in and around the vessels.
MPA affects smaller vessels. In both diseases, an antibody called ANCA (Anti-Neutrophil Cytoplasmic Antibody) is present; hence, the diseases are referred to as ANCA-associated diseases.

6.2 How common is it? Is the disease in children different from the disease in adults?

GPA is an uncommon disease, especially in childhood. The true frequency is not known but it probably does not exceed 1 new patient in 1 million children per year. More than 97% of reported cases occur in the white (Caucasian) population. Both sexes are affected equally in children, whereas in adults men are affected slightly more often than women.

6.3 What are the main symptoms?

In a large proportion of patients, the disease presents with sinus congestion that does not improve with antibiotics and decongestants. There is a tendency for crusting of the nasal septum, bleeding and ulcerations sometimes causing a deformity known as saddle-nose. Airway inflammation below the vocal cords can cause narrowing of the trachea, leading to a hoarse voice, nosebleeds, chronic ear

inflammation mimicking infection), and respiratory problems. The presence of inflammatory nodules in the lungs results in symptoms of pneumonia with shortness of breath, cough and chest pain.
Kidney involvement is initially present in only a small proportion of patients but it becomes more frequent as the disease progresses, causing abnormal urine findings and blood tests for kidney function, as well as hypertension. Inflammatory tissue can accumulate behind the eye balls, pushing them forward (protrusion), or in the middle ears, causing chronic otitis media. General symptoms such as weight loss, increased fatigue, fevers and night sweats are common, as are various skin and musculoskeletal manifestations.
In MPA, the kidney and lungs are usually the main organs affected, although any organ can be affected.

6.4 How is it diagnosed?

Clinical symptoms of inflammatory lesions in upper and lower airways, together with kidney disease, typically manifested by the presence of blood and protein in the urine and increased blood levels of substances cleared by the kidneys (creatinine, urea), are very suspicious of GPA. Blood tests usually indicate increased non-specific inflammatory markers (ESR, CRP) and elevated ANCA titers. The diagnosis may be supported by a tissue biopsy.

6.5 What is the treatment?

Corticosteroids in combination with cyclophosphamide are the mainstay of the induction treatment for childhood GPA/MPA. Other agents suppressing the immune system, such as rituximab, can be chosen according to the individual situation. Once disease activity settles, it is kept under control with "maintenance therapy", usually with azathioprine, methotrexate or mycophenolate mophetil.
Additional treatments include antibiotics (commonly long-term co-trimoxazole), blood pressure lowering agents, drugs against blood clot formation (aspirin or anticoagulants) and painkillers (non-steroidal anti-inflammatory drugs, NSAIDs).

7. PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

7.1 What is it?

Primary Angiitis of the Central Nervous System (PACNS) in childhood is an inflammatory brain disease targeting small or medium blood vessels of the brain and/or spinal cord. Its cause is unknown, although in some children, previous exposure to varicella (chickenpox) raises the suspicion that there is an infection-triggered inflammatory process.

7.2 How common is it?

It is a very rare disease.

7.3 What are the main symptoms?

The onset may be very sudden weakness of limbs (stroke), movement disorder, difficult-to-control seizures, severe headaches, and confusion. Sometimes more diffuse neurological or psychiatric symptoms, such as mood and behaviour changes, may be presenting symptoms. Systemic inflammation causing fever and elevated blood inflammatory markers are commonly absent.

7.4 How is it diagnosed?

Blood tests and cerebrospinal fluid analysis ("lumbar puncture") are non-specific and are mainly used to exclude other conditions that might present with neurological symptoms such infections, other non-infectious brain inflammatory diseases or blood clotting disorders. Brain or spinal cord imaging techniques are the main diagnostic investigations. Magnetic resonance angiography (MRA) and/or conventional angiography (X-rays) are commonly used to detect involvement of medium and large arteries. Repeated investigations are needed in order to assess disease evolution. When artery involvement is not detected in a child with progressive unexplained brain lesions, small vessel involvement should be suspected. This can be eventually confirmed by a brain biopsy.

7.5 What is the treatment?

For post-varicella disease, a short course (about 3 months) of

corticosteroids is usually sufficient to halt disease progression. If appropriate, an anti-viral drug is also prescribed (acyclovir). Such a course of corticosteroids may only be needed for the treatment of angiography-positive non-progressing disease. If the disease progresses (i.e. brain lesions are getting worse), then intensive treatment with immunosuppressive drugs is vital to prevent further brain damage. Cyclophosphamide is used most commonly in the initial acute disease and then is replaced by maintenance treatment (e.g. azathioprine, mycophenolate mophetil). Drugs that affect blood clot formation (aspirin or anticoagulants) should be considered.

8. OTHER VASCULITIDES AND SIMILAR CONDITIONS

Cutaneous leukocytoclastic vasculitis (also known as hypersensitivity or allergic vasculitis) usually implies a blood vessel inflammation caused by a reaction to a sensitising source. Drugs and infections are common triggers of this condition in children; commonly, however, no obvious trigger is identified. It usually affects small vessels and has a specific microscopic appearance in the skin biopsy.

Hypocomplementaemic urticarial vasculitis is characterised by a rash that is often itchy, widespread and resembling hives that does not fade as quickly as a common skin allergic reaction. Blood findings of a decreased level of complement (a blood protein) accompany this condition.

Eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg-Strauss syndrome) is an extremely rare type of vasculitis in children. Various vasculitis symptoms in the skin and internal organs are accompanied by asthma and increased numbers of a type of white blood cell known as eosinophils in blood as well as in tissues.

Cogan´s syndrome is a rare disease characterised by the involvement of eyes and inner ears with photophobia, dizziness and hearing loss. Symptoms of more widespread vasculitis may be present.

Behçet’s disease has been discussed separately in another section.