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Driesen Yentl, MD (1), Verweij Marjoke, MD, PhD (1), De Maeseneer Marianne, MD, PhD (2), De Dooy Jozef, MD, PhD (3), Wojciechowski Marek, MD (1), Van Den Akker Machiel, MD (4)

(1) Department of Pediatrics, Antwerp University Hospital, Antwerp, Belgium

(2) Department of Dermatology, Erasmus MC, Rotterdam, Netherlands and Faculty of Medicine and Health Sciences, Antwerp University, Antwerp, Belgium

(3) Pediatric Intensive Care, Antwerp University Hospital, Antwerp, Belgium

(4) Pediatric Hematology, ZNA Queen Paola Children's Hospital, Antwerp, Belgium

Corresponding author: Yentl Driesen, Universitair Ziekenhuis Antwerpen, Afdeling Pediatrie, Wilrijkstraat 10, 2650 Edegem, Belgium. Fax number: 00323/829.11.94. Telephone number: 00323/821.31.82. E-mail: yentl.driesen@uza.be or marek.wojciechowski@uza.be

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Abstract

Stroke and deep venous thrombosis are rare complications of varicella zoster infection. We report three cases of children with a stroke and one case of a boy with a deep venous thrombosis after recent chicken pox.

Text

Introduction

Well known complications of varicella zoster virus (VZV) infection or chickenpox include secondary bacterial infections (most frequently *Staphylococcus* or *Streptococcus*), varicella pneumonia and central nervous system complications such as varicella encephalitis and cerebellitis.[1] Vascular complications of varicella zoster infections are rare but serious. Mainly two types have been described in literature: first, arterial vasculitis and thrombosis, which occur mostly in the central nervous system,[2-4] and second, deep venous thrombosis (DVT), whether or not associated with pulmonary embolism or purpura fulminans.[5-8]

We describe three cases of children with an arterial intracerebral thrombosis and one case of a 1-year old patient with extensive DVT, all with varicella infection in the recent history. In addition a review of the current medical literature is presented.

Case 1

A two year old boy presented to the emergency room because of an acute right-sided hemiparesis, right-sided facial palsy with a ptosis, and a speech disorder. The day before admission he received a Pneumococcal and hexavalent (combined Diphteria/Tetanus/acellular Pertussis-Inactivated Polio – *Haemophilus influenzae* – Hepatitis B) vaccine. Three months earlier he had an apparently uncomplicated varicella infection. The boy was previously healthy, except for a food allergy. Family history did not reveal any relevant information.

Laboratory investigations, including complete blood count (CBC), C-reactive protein (CRP), liver function tests, kidney function and electrolytes, were all normal. Serology for Mycoplasma and Borrelia was negative. Computed tomography (CT) of the brain showed no abnormalities, while the magnetic resonance imaging (MRI) revealed a recent infarction of the crus posterior of the left capsula interna, compatible with an occlusion of the left arteria

choroidea anterior (figure 1). Lumbar puncture (cell count, protein, glucose) was normal. Electroencephalography and echocardiography were normal. Extensive coagulation investigation (activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, D-dimers, thrombin time, Factor II, Factor V, Von Willebrand activity and antigen, Factor XI, antithrombin III, protein C activity, APC resistance, protein S activity, circulating anticoagulans, lupus anticoagulans, platelet function tests and homocysteine) was normal and lupus anticoagulans was negative.

Treatment with intravenous methylprednisolone (1 mg/kg/day) and oral acetylsalicylic acid (5 mg/kg/day) was started. Intravenous acyclovir (30mg/kg/day) and cefotaxime (200mg/kg/day) were given until the cerebrospinal fluid (CSF) culture and polymerase chain reaction (PCR) for herpes simplex were reported negative. The boy improved quickly with complete neurologic recovery at discharge after five days. Methylprednisolone and acetylsalicylic acid were stopped at discharge. Follow-up MRI after two months showed no sequelae.

Case 2

A one and a half year old boy was brought to the emergency department with a right-sided hemiparesis since one day. Medical history reported a varicella infection eight months before admission. No other problems in personal or family history were noted.

Laboratory investigations showed normal CBC, CRP, kidney and liver function; CT cerebrum did not show any signs of bleeding or increased intracranial pressure. The MRI of the brain revealed a (sub)acute ischemic lesion in the left corona radiata and nucleus lentiformis compatible with the deep arteria cerebri media territorium (figure 2).

PCR varicella on CSF was weakly positive. Anti-VZV IgG in serum was positive. Echocardiography was normal. Extensive coagulation investigation (activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, D-dimers, prothrombin

G20210A mutation, antithrombin III, protein C activity, APC resistance, protein S activity, platelet function tests and homocysteine) was normal and lupus anticoagulans was negative. Metabolic screening for amino acids and organic acids was also normal. Treatment with ceftriaxone (100 mg/kg/day until negative cultures were reported), acyclovir (30 mg/kg/day for two weeks) and methylprednisolone (1 mg/kg/day for five days) was immediately started. Due to the severity of the neurologic deficit, in anticipation of the results, subcutaneous enoxaparin (2mg/kg/d until discharge) was added to the therapy. Symptoms slowly improved during hospitalization. The patient was discharged with aspirin (for a total period of two years). MRI-angiography, performed a month after discharge, showed the ischemic injury without residual stenosis or significant irregularities of the left arteria cerebri media.

Case 3

A three year old girl was admitted to the hospital because of a progressive paresis of the right arm, dysarthria and a right facial palsy during several days. Medical history revealed a varicella infection 6 weeks before admission. Family history revealed the presence of a long QT syndrome in the mother. Laboratory investigations resulted normal CBC, CRP, kidney and liver function and coagulation tests. She had positive anti-VZV IgG in serum and a negative IgM. PCR varicella on CSF was positive. MRI of the brain revealed ischemic lesions in the left parietal region, in the corona radiata and nucleus lentiformis compatible with an occlusion of the left arteria cerebri media (figure 3). Echocardiography and electrocardiography were normal. Treatment with intravenous acyclovir (30 mg/kg/day for two weeks), methylprednisolone (1 mg/kg/day for five days) and oral aspirin (after a loading dose, 25 mg/day for two years) was started. There was a good clinical evolution. The neurological abnormalities recovered completely over the following months.

Case 4

A previously healthy one year old boy was admitted to the emergency department with an acutely swollen, cyanotic very painful left leg and a cold left foot. The perimeter of the thigh and calf were 5 cm more than the contralateral leg. The child did not move the left leg spontaneously. Since four days he suffered from a varicella infection with high fever. Family history was negative.

Initial laboratory investigations showed anemia (hemoglobin 9,7 g/dL), leukocytosis ($16{,}2.10^9$/L) with neutrophilia ($11{,}66.10^9$/L), normal thrombocyte count, increased CRP (275,0 mg/L), elevated liver transaminases (AST 95 U/L, ALT 50 U/L), elevated D-dimers (47,4 µg/mL) and a prolonged activated partial thromboplastin time (aPTT 57,3 sec). Duplex ultrasound revealed a DVT extending from the calf veins, over the popliteal vein and femoral vein to the common femoral vein, which was still partially obstructed up to the saphenofemoral junction. The profunda femoral vein was also obstructed by acute thrombus. Treatment was immediately started with subcutaneous low molecular weight heparin (LMWH; nadroparin in a therapeutic dose of 450 IE/kg/d) and intravenous antibiotics (penicillin and clindamycin), because of suspected *Streptococcus* septicemia. Blood culture indeed showed growth of *Streptococcus pyogenes*.

The next day, clinical evolution appeared to be unfavorable – presenting as a real phlegmasia caerulea dolens (see Figure, Supplemental Digital Content 1: clinical picture of phlegmasia caerulea dolens of the left leg in our patient) and therefore it was decided to start with intravenous thrombolysis with recombinant tissue plasminogen activator (alteplase). In addition, a short-stretch bandage was applied to the left leg. Thrombolysis could be switched to intravenous unfractionated heparin after 48 hours. The swelling of the leg had decreased considerably and the child could move normally again. Four days later, oral anticoagulants (warfarin, starting dose 0,2 mg/kg) were started. However, since the effect on the INR was

extremely variable, treatment was switched to subcutaneous LMWH (nadroparin, 450 IE/kg/d), which was continued for four more months. Unfortunately duplex ultrasound revealed persisting occlusion of the femoral vein and popliteal vein, with collateral circulation mainly via the great and small saphenous veins.

Initial coagulation investigation showed a decrease in protein C (34%, normal range 65-127%), protein S (20%, normal range 67-136%) and antithrombin III (78%, normal range 101-131%) and a positive lupus anticoagulans. Homocysteïne, fibrinogen and Factor VIII were normal. APC resistance was absent. After two months protein C (60%) and antitrombin III (103%) had normalized, and lupus anticoagulans had become negative. However Protein S activity levels remained low (36%) two months after LMWH treatment had been stopped, leading to the diagnosis of underlying hereditary protein S deficiency.

Discussion

These four cases presented with vascular complications related to previous varicella infection. In the literature varicella vasculopathy includes arterial ischemic stroke[2-4,9,10] as well as DVT.[5-8] The risk for both arterial and venous occlusion as complication of a varicella infection is significantly elevated in patients with congenital disorders of coagulation, such as protein S or protein C deficiency, and homozygous carriers of factor V Leiden or Methylene Tetrahydrofolate Reductase mutation; [5,11-14] as well as in patients with concomitant sepsis.[15] Other risk factors for thrombotic complications associated with varicella infection include diabetes mellitus type 1, patent foramen ovale, severe iron deficiency anemia, Down syndrome and AIDS.[13]

Arterial complications

Arterial ischemic stroke was first described in the years 1980 by Eda *et al*. and Kamholz *et al.* [2,3] They reported several cases with acute hemiparesis after a VZV infection. Cerebral imaging revealed ischemic lesions in the internal capsule and angiographic evidence of vasculitis.

After a primary VZV infection the virus becomes latent in the nerve ganglia. It is thought that the virus invades the central nervous system by transaxonal spreading into the media layer of the cerebral arteries.[16-18] In these arteries an inflammatory process is triggered, characterized by the accumulation of inflammatory cells (predominantly neutrophils) and smooth muscle cells, resulting in thickening of the vessel wall, endothelial dysfunction and changed nitric oxide metabolism. This leads to the typical vasculitis with a changed arterial caliber and contractility.[17,18]

It is estimated that post varicella arteriopathy (PVA) accounts for one third of the pediatric strokes.[4,19] The incidences mentioned vary strongly among different authors: Ichiyama *et al.* [20] report one stroke in 6500 varicella cases, Askalan *et al*. of one in 15.000 cases.[4] However, no exact incidence rate is known. PVA typically affects previously healthy children under the age of 10 years (mean age approximately 5 years), generally within the first 6 months after VZV infection.[13,18,21-23]

PVA often presents as an acute hemiparesis (91%). Other symptoms can include speech disorders, facial palsy, ataxia, lethargy, headache, convulsions and vomiting.[13,23,24]

Diagnosis of PVA is still a challenge. MRI findings reveal most often infarction of the basal ganglia and/or internal capsule, but also cerebral or thalamic ischemic lesions can be seen. This is accompanied by focal or multifocal stenosis of the proximal parts of the anterior and medial cerebral arteries. However, these findings are not specific and can also be found in other

types of vasculitis.[4,13,23,25] Evaluation of CSF might be helpful but is not always conclusive. In adult patients, PVA can be ruled out if VZV markers (PCR for VZV DNA and VZV IgG antibodies) are negative in CSF.[19,26] However, this is less clear in the pediatric population and in a substantial part of these patients no markers are detected in the CSF.[24]

There is no consensus about the treatment of these arterial ischemic strokes.[24,27] Some authors recommend treatment with anticoagulants or platelet antiaggregants because of the risk of recurrence.[18,23,24] Prednison or methylprednisolone are often used in order to affect the inflammatory process, generally 1 mg/kg/day for five days.[19] However, they should be used with caution because of the risk of viral reactivation.[10] Most authors also recommend the use of high doses of acyclovir, because VZV DNA is found in the CSF in many cases suggesting viral replication.[19,24,27] There is no consensus about optimum dose and duration of antiviral treatment. Gilden *et al*.[19] suggest treatment with intravenous acyclovir, 10-15 mg/kg/dose, three times daily for a minimum of 14 days. Regardless the chosen treatment, (nearly) complete recovery is to be expected. Even without therapy most authors report a monophasic course in most patients with complete recovery in 50% of cases[13,18], Miravet *et al*. however report complete resolution in only a minority of patients, their study showed an improvement of arteriopathy in half the cases, whereas the other half of MRI abnormalities remained static or progressed.[25] Dunkhase-Heinl *et al.* describe mild motor and cognitive deterioration in three out of four cases. [24]

Venous thromboembolic complications

Deep venous thrombosis is perhaps an even less frequent consequence of varicella. To date its incidence is unknown. The oldest reference we could find was made by Fondu *et al.* and dates from 1968.[28] Certain viral infections, including varicella, may give rise to a transient presence of lupus anticoagulans and/or antiphospholipid antibodies in the blood.[6,29-33] Varicella can

also be associated with the development of an acquired protein S deficiency caused by autoantibodies.[6,8,32-34] Several authors describe the production of IgG and/or IgM antibodies against protein S as a reaction to a VZV infection.[6,7,15,32,35] The deficiency is not caused by an inhibition of protein S, but rather by an increased clearance out of the blood.[6,31,32] This strongly reduces the antithrombotic function of protein S, leading to a prothrombotic state.

The degree of protein S deficiency is thought to be a determining factor in the development of thrombi. In addition, a number of contributing features is described: for example the simultaneous occurrences of a heterozygous phenotype for factor V Leiden and a secondary infection with *Streptococcus*.[6,11,15] Varicella with DVT was also described in a number of children with congenital protein C and S deficiency and APC resistance. Lack of these coagulation controlling factors can, apart from DVT, lead to purpura fulminans.[8] Another hypothesis is that the thrombosis is caused by direct damage by the varicella virus to the endothelial cells of the involved blood vessels. This leads to platelet aggregation and therefore formation of thrombi.[36]

Since venous complications are caused by a thrombotic process due to a deficient antithrombotic factor, most authors recommend treatment with therapeutic doses of heparin either unfractionated or LMWH.[5,7,32] If there is insufficient response to this therapy, correction of deficiencies with infusion of protein S or C concentrates or fresh frozen plasma can be given.[5,6,8,33] In very severe cases even plasmaferesis, with replacement of losses by fresh frozen plasma, is described to remove the circulating auto-antibodies.[8,33] Protein S concentrates are less efficient since the administered protein S is also exposed to the elevated clearance.[7] Some authors also recommend the use of steroids and immunoglobulins to stop the production of auto-antibodies; these treatments should be used with caution since they increase the risk of fungal or bacterial surinfections, certainly in children who have extensive skin lesions due to purpura fulminans.[8,33] A consensus about the methylprednisolone dosage is

still lacking.[8] After several months the anti-protein S antibodies as well as the lupus anticoagulans usually disappear.[6]

In our first three patients the stroke was presumably caused by a vasculitis as a result of the varicella infection in the recent history. They were treated with acyclovir, corticosteroids and anticoagulant/anti-platelet therapy. All of them had a favorable clinical evolution with regression of symptoms. In our fourth patient, the cause of DVT was probably multifactorial and a result of the combination of congenital protein S deficiency, active varicella infection, and streptococcal sepsis.

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Figures

Figure 1. MRI: recent infarction of the crus posterior of the left capsula interna, compatible with an occlusion of the left arteria choroidea anterior. Left: T2-weighed image. Right: Flair-image.

Figure 2: Acute and subacute ischaemic lesions in de corona radiata and nucleus lentiformis left compatible with the deep left arteria cerebri media territorium. Left: T2-weighed image. Right: Flair-image.

Figure 3: Several (sub)acute lesions in the left arteria cerebri media territorium, both in the parietal region, as well as in de corona radiata and the nucleus lentiformis. Left: T2-weighed image. Right: Flair-image.