Acute ischemic stroke secondary to childhood primary angiitis of cerebral nervous system (cPACNS) - case report and literature review

Udar niedokrwienny mózgu w przebiegu dziecięcego pierwotnego zapalenia naczyń ośrodkowego układu nerwowego (cPACNS) - opis przypadku i przegląd literatury

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ABSTRACT

Introduction: Primary angiitis of central nervous system in childhood (cPACNS) is a rare idiopathic inflammatory disease and an increasing cause of acute ischemic stroke in children. Due to heterogenous classification and poorly understood pathomechanism there are no estimated prevalence and treatment guidelines for PACNS in pediatric population.

Case report: A 6-year-old boy with symptoms of acute ischemic stroke was admitted. Neurological examination revealed left hemiparesis. After exclusion of brain hemorrhage the patient was primarily treated with anticoagulants. Brain magnetic resonance (MRI) showed reduced flow with longitudinal stenosis in right internal carotid artery and right middle cerebral artery. Numerous ischemic focuses acute and chronic were found in right cortical and subcortical regions. Hematologic disorders were excluded, as were other inflammatory disorders. Due to imaging studies and clinical features primary angiitis was suspected. Corticosteroids were administrated and regression of neurological deficits was observed. Eventually cPACNS was diagnosed.

Conclusion: cPACNS should be considered after exclusion of systematic, rheumatological and secondary causes of vasculitis. Fast diagnosis and administration of therapy is absolutely essential as most of the case series carried on adult population suggest a favorable clinical outcome of cPACNS early treated with steroids.

Key words: stroke, children, PACNS, vasculitis, inflammation

STRESZCZENIE

Wstęp: Dziecięce pierwotne zapalenie naczyń ośrodkowego układu nerwowego (ang. childhood primary angiitis of cerebral nervous system, cPACNS) jest rzadką, idiopatyczną chorobą zapalną. Jej rozpoznawalność w populacji dziecięcej wzrasta, jednak ze względu na brak jednoznacznej klasyfikacji zachorowalność w grupie pediatrycznej wciąż pozostaje nieznana. Patofizjologia choroby jest słabo poznana, co przyczynia się do braku wytycznych dotyczących leczenia.

Opis przypadku: 6-letni chłopiec został przyjęty z objawami ostrego udaru niedokrwiennego mózgu. Przy przyjęciu w badaniu neurologicznym stwierdzono masywny niedowład połowiczy lewostronny. Po wykluczeniu krwotoku śródmózgowego włączono leczenie przeciwzakrzepowe. Badanie rezonansu magnetycznego mózgowia z funkcją angiografii (angio-MRI) wykazało redukcję przepływu i podłużne zwężenia w prawej tętnicy szyjnej wewnętrznej i prawej tętnicy środkowej mózgu. Liczne ogniska niedokrwienne, zarówno ostre jak i przewlekłe, zostały uwidocznione w regionach korowych i podkorowych obu półkul mózgu. Obraz radiologiczny odpowiadał pierwotnemu zapaleniu naczyń mózgowia. W trakcie procesu diagnostycznego wszelkie zaburzenia hematologiczne, jak i zapalenia tętnic na tle wtórnym zostały wykluczone. Ze względu na obraz MRI włączono leczenie sterydami, co spowodowało stopniową regresję deficytów neurologicznych, a także poprawę przepływu przez zwężone tętnice uwidocznioną w badaniu obrazowym. Ostatecznie postawiono rozpoznanie pierwotnego zapalenia naczyń mózgu (cPACNS).

Podsumowanie: cPACNS powinno być podejrzewane u pacjentów z charakterystycznymi, podłużnymi zmianami w obrębie naczyń mózgowia, u których wykluczono wtórne przyczyny zapalenia naczyń. Szybka diagnoza i włączenie terapii są kluczowe dla regresji zmian neurologicznych i powrotu pacjenta do pełnej sprawności.

Słowa kluczowe: udar, dziecko, zapalenie naczyń, zapalenie

INTRODUCTION

Acute ischemic stroke (AIS) in pediatric population is a rare disease with the estimated incidence of 1-6 per 100,000. The diagnosis is severe, mortality ranges from 7% to 28%, around 50% of children have persistent neurological and cognitive deficits which significantly lower their life quality [1, 2]. The pathogenesis, symptoms and differential diagnosis differ from those ones in adults. Several underlaying factors as: congenital heart diseases, infections, hematologic disorders, primary and secondary cerebral arteriopathies were identified. One of the recently growing recognition of pediatric AIS is childhood primary angiitis of the central nervous system (cPACNS). cPACNS is a rare idiopathic inflammatory disease, affects mostly parenchymal and leptomeningeal vessels, less frequently veins and venules. Classification of cPACNS was con-

structed analogous to the CASCADE Criteria (Childhood AIS Standardized Classification and Diagnostic Evaluation) and contains four subtypes depending on vessel size and different clinical course [3–5]. Currently there are no other incidence rates of cPACNS [5–7]. In a study performed by Fullerton et.al, the prevalence of PACNS causing presentation with AIS was estimated in 24% however only 50% of the patients had vascular imaging so the true prevalence might be underestimated [6]. This report presents a case of pediatric patient diagnosed with primary angiitis of the central nervous system (cPACNS) leading to acute ischemic stroke.

CASE REPORT

A 6-year-old boy with no medical history was admitted with left hemiparesis which appeared after sport exercises. The day before the patient had an acute headache. Neurological examination revealed pyramidal syndrome with the left side hyperreflexia, partial paresis of the left upper limb (MRC muscle scale=2), total paresis of the left lower limb (MRC=0) and central paresis of the left facial nerve. Clinical presentation suggested ischemic stroke of the right hemisphere.

MRI showed reduced flow in the right internal carotid artery (ICA) and right middle cerebral artery (MCA) with longitudinal stenosis of the vessels and slightly thickness of the wall (Figure 1). Numerous ischemic focuses, acute and chronic, were found in the right cortical and subcortical regions. Computer tomography with angiography revealed right ICA narrowing in C2 region to 1,2 millimeters.

Hematologic disorders were excluded as morphology, fibrinogen, level of coagulation factors, von Willebrand factor, antithrombin level, homocysteine, protein C and S were within the norm. Leiden V and prothrombin mutations were excluded. C-reactive protein (CRP) was low. Anti-beta-2-glycoprotein antibodies and lupus anticoagulant were undetectable. Echocardiography did not reveal any cardiological disorders.

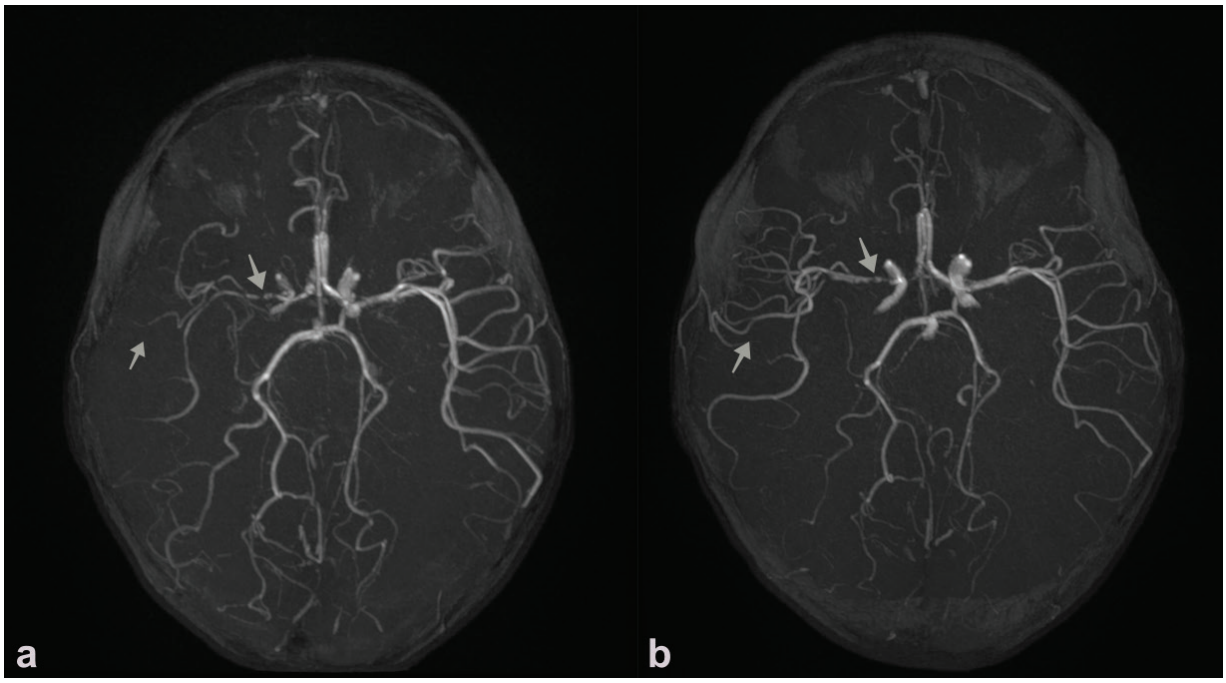
The imaging studies suggested vessels inflammation as a cause. ANCA and ANA antibodies were negative. Hepatitis B and C, HIV and mononucleosis antibodies were not detected. Tuberculosis was excluded as the Quantiferon was negative. Antibodies against Varicella-Zoster Virus (VZV) were remarkable in IgG class, presenting level 2081 mUI/ml. Antibodies in class IgM were negative. Eventually the cPACNS was diagnosed.

Patient was treated with anticoagulants. Enoxaparin was administrated with accordance to anti-Xa level. Slight regression of paresis was observed. Due to the suspicion of an inflammatory disease, steroid therapy was added with five infusions of methylprednisolone, 500mg each. Motor improvement was reveled with score MRC=3 in the upper limb and MRC=4 in the lower limb. The patient was discharged with prednisone 2x20mg and enoxaparin 2x20mg per day. Further rehabilitation was recommended.

3- month follow-up

MRI follow-up did not reveal new ischemic changes. Stenosis in RICA and right MCA were observed, but with a slight improvement compared to previous examination. Better perfusion of the right cortical region was observed. Clinically, further regression of paresis was observed in the upper limb MRC=4, in the lower limb MRC=5. Spasticity was reveled in both limbs.

Figure 1 MR angiography showing longitudinal stenosis of right MCA (a). Second image (b) after two months of steroid therapy. Stenosis reduction and better perfusion of right cortical region can be seen.
Rycina 1 *Angiografia MRI ukazująca podłużne zwężenia w zakresie prawej MCA (a). Drugie zdjęcie (b) wykonane po dwóch miesiącach sterydoterapii. Widoczna redukcja stenozy i lepszy przepływ w regionie korowym prawej półkuli*



DISCUSSION

The main pathophysiological mechanism of PACNS includes infiltration of vessel walls with immune cells. This may result in thickening of the vessel walls and alternating sections of stenosis, which contribute to poor blood circulation [8, 9]. Types of PACNS were distinguished depending on vessel diameter: large and medium – angiography-positive (AP-PACNS) and angiography-negative small vessel PACNS (AN-PACNS). AP-PACNS divides on non-progressive forms (APNP-PACNS) and progressive forms (APP-PACNS). APNP-PACNS is believed to be the most common type of disease [3]. The frequency of PACNS in adult population of North America was estimated to be 2.4/1.000.000 per year with a slight male predominance [9]. Approximately 50% of patients are between 40-60 years old with the peak in the sixth decade of life, but the vasculopathy may occur at any age [8]. There is no incidence rate for cPACNS but the number of cases described has increased what suggests cPACNS to be an important, but underestimated, cause of strokes in children [7].

Clinical features

Diagnostic criteria for PACNS were proposed by Calabrese and Malek et al. for adult population and adopted by pediatric rheumatologists to use in childhood PACNS[10, 11]. They consist of:

1. A newly acquired focal and/or diffuse neurologic deficit and/or psychiatric symptoms in a previously healthy child aged ≤ 18 years
2. Evidence of cerebral vasculitis on angiography or brain biopsy
3. No evidence of systematic vasculitis or any disorder that may mimic or cause features and signs of angiitis.

However, there are various definitions and sometimes contradictory terminology of AIS among different clinicians. To unify the nomenclature and clarify recognition of AIS among children The International Pediatric Stroke Study proposed a consensus-based classification system: the CASCADE criteria (Childhood AIS Standardized Classification and Diagnostic Evaluation). Primary classification contains seven subtypes: small vessel arteriopathy, focal cerebral arteriopathy (FCA), the bilateral cerebral arteriopathy of childhood, the aortic/arteriopathy, cardioembolic, other, and multifactorial. Seven Secondary criteria describe etiology: genetic, infectious, Hematologic/thrombotic, inflammatory, genetic/ metabolic (mitochondrial cytopathy), drug/toxin exposure and prolonged vasospasm. The last section of CASCADE criteria describes temporality of clinical features: progressive, stable and reversible arteriopathy. In accordance with the CASCADE classification, our patient should be diagnosed with FCA with primary CNS vasculitis etiology [4].

Clinical presentation is heterogenous and depends on the cPACNS subtype. Stroke and headache are the most common clinical presentations of angiography positive, large and medium vessels. (AP-PACNS). Usually decreased blood flow due to stenosis caused by vessel wall inflammation manifests itself as sudden-onset focal neurologic deficits, such as aphasia, visual disturbance, hemiparesis, ataxia, hemifacial weakness, hemisensory loss and fine motor skill loss. Approximately 40% of children have headaches which is the most common presenting feature and in around 10% decreased cognition and behavior changes are present [10].

Laboratory Studies

There are no specific changes for PACNS in laboratory parameters. In the most common type of PACNS-APNP, the results of CSF are usually normal, uncommonly it may reveal mild pleocytosis and increased protein level [5]. The CSF analysis can be used in order to eliminate other possible causes of the symptoms (Tab. I) [9]. Blood tests are usually within the norm. Markers of systemic inflammation like CRP and erythrocyte sedimentation rate are frequently normal [12]. In APP-PACNS changes in CSF can be found in 50% of patients and they are manifesting with elevated protein, pleocytosis and elevated intracranial pressure. Children affected by AN-PACNS typically show elevated levels of inflammatory markers and C3. Also, in one third children with this subtype the presence of oligoclonal bands in CSF has been noticed [7]. Because angiography studies are negative in this group of patients, the biopsy of targeting lesions is suggested. Perivascular lymphocytic infiltration can be observed [5].

Blood and serum analysis of our patient did not show any significant abnormalities. The widen antibodies panel was performed to exclude secondary causes of vasculitis. Rheumatological diseases presenting with vasculopathies such as Kawasaki disease, Takayasu disease or lupus erythematosus need to be excluded. Vasculopathies caused by systematic disease such as mononucleosis or hepatitis should be considered during diagnosis.

Imaging studies

The gold standard imagining method is MRI with sensitivity of 90-100%, but remains non-specific [7]. The most common findings are multifocal infarcts which are typically bilateral, distal, and across multiple vascular territories, leptomeningeal and parenchymal enhancement [12]. Other neuroimaging techniques used are MR angiography and computed tomography, however they are less sensitive. Both of these methods are useful in investigating large proximal arteries, while PACNS can also affects medium to small vessels [12]. Method which has better resolution in accessing medium vessels is digital subtraction angiography (DSA). It allows for imaging the vessels to lumen diameter over 0.2mm, but direct evaluation of the vessel wall is unviable. The typical angiography finding is called beading. Beading refers to alternating segments of stenosis and dilatation. Less popular findings include focal occlusions, collateral circulation and microaneurysms, mass effect, delayed transit time, or cuffing. Due to higher radiation exposure and invasive character, DSA is used infrequently [12].

Tab. I Differential diagnosis of PACNS
Diagnostyka różnicowa cPACNS

Differential diagnosis of cPACNS	
Systematic rheumatic diseases with CNS manifestation	Takayasu arteritis, polyarteritis nodosa, Kawasaki disease, Henoch-Schoenlein purpura, Bechet disease, granulomatosis with polyangiitis, microscopic polyangiitis, systematic lupus erythematous
Secondary vasculitis	Infections (for example CMV, HBV, HCV, HIV), drugs, malignancy
Coagulation pathologies	Leiden V mutations, APC, coagulation factors deficiency
Reversable vasoconstriction syndrome	
Neurometabolic diseases	homocystinuria, Fabry disease
Genetic	NOTCH3, COL4A1, MOPD2
Structural vasculopathy	arterial dissection, arteriovenous malformations, aneurysm, cavernous malformations, Moyamoya disease

Therapy

Presently, there is no evidence-based guidelines therapy for cPACNS [5]. Treatment options typically consist of corticosteroids, cyclophosphamide, antiplatelet agents and immunosuppressant drugs. The aim of long-term treatment is to prevent recurrences of AIS and/or neurocognitive impairment. In suspected cPACNS the use of low-dose acetylsalicylic acid (ASA) is recommended in prevention of relapses of AIS, ASA is also used in acute treatment shorter than 1 week when there is an incidence of cPACNS with AIS. In confirmed cPACNS treatment may include low-molecular-weight heparin (LMWH), such as enoxaparin or unfractionated heparin (UFH) at therapeutic doses. In chronic anticoagulant therapy the usage of a combination ASA for ≥2 years with clopidogrel for 6–12 months is suggested [5]. Anti-Inflammatory therapy relies on corticosteroids alone in non-progressive cPACNS and in a combination with pulses of cyclophosphamide in the progressive type of the disease [7].

CONCLUSIONS

Vasculopathies can be an underestimated cause of stroke in children population. All changes in angiography should be considered as vasculitis. Differential diagnosis should cover rheumatological, systematic and secondary causes. After exclusion, the primary angiitis of central nervous system can be suspected. Fast diagnosis and administration of therapy is absolutely essential, as most of the case series suggest a favorable clinical outcome of cPACNS early treated with steroids.

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