



Short Communication

An ischemic stroke as the presenting manifestation of rapidly progressive primary angiitis of central nervous system in a 17-year-old boy

Zinovia-Maria Kefalopoulou^{a,*}, Stamatis-Nick Liossis^b, Theodora Sagona^a, Dimitra Veltsista^a, Petros Zampakis^c, Pantelis Kraniotis^c, Aikaterini Solomou^c, John Ellul^a, Elisabeth Chroni^a^a Department of Neurology, Patras University Hospital, Patras, Greece^b Department of Rheumatology, Patras University Hospital, Patras, Greece^c Department of Radiology, Patras University Hospital, Patras, Greece

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ABSTRACT

Background: Childhood primary angiitis of the central nervous system (cPACNS) is an increasingly recognized inflammatory brain disease in children.**Case presentation:** We present a case of a 17-year-old boy with recurrent ischemic events over a short time period. Diagnosis of angiography positive cPACNS was made based on neuroimaging findings while secondary causes or mimics of CNS vasculitis were meticulously excluded. The patient exhibited rapid deterioration of his condition with poor initial response to immunosuppressive treatment.**Conclusions:** Recognition of cPACNS remains a challenge because of rarity of disease, unexplained etiopathogenesis, protean clinical presentation, as well as lack of specific laboratory and neuroimaging markers.

1. Introduction

Primary angiitis of the central nervous system (PACNS) is a rare and debilitating disorder characterized by inflammation and destruction of CNS vessels, without evidence of systemic vasculitis (Calabrese and Mallek, 1988). PACNS typically arises in the fourth or fifth decade of life, with an estimated incidence of 2.4 cases per 1,000,000 person-years (Salvarani et al., 2007). The occurrence of PACNS in patients under the age of 18, namely childhood PACNS (cPACNS), has been increasingly recognized. The exact incidence remains unknown, in view of the paucity of data on cPACNS in the literature. The clinical spectrum is highly variable and nonspecific, including headaches, cognitive dysfunction, seizures, and focal neurologic deficits. Diagnosis of cPACNS relies on confirmatory MRI and angiographic findings, while excluding an underlying systemic condition (Benseler et al., 2006). Hence, early recognition and timely management that may warrant a complete neurological recovery, present as significant challenges for

the treating physicians. We present here the diagnostic and treatment related challenges in a case of a young boy who was diagnosed with cPACNS in our institution.

2. Case report

A 17-year-old boy, with no past medical or neurological family history, presented with mixed aphasia, right-sided hemiparesis (4+/5 strength) and right central facial palsy of acute onset, 4–5 h before admission. Plantars were flexor. Involuntary choreiform movements, with stereotypies of right upper limb and face, were also present. Eye movement, lower cranial nerve and sensory examinations were normal. There were no signs of cerebellar dysfunction or meningismus. He had a mild 3-day prodrome phase with diarrhoea and fever (< 38 °C). There was no history of headaches, altered consciousness, or head/neck trauma. Either a cerebrovascular event or CNS infection was suspected.

Routine laboratory workup was unremarkable apart from a

Abbreviations: PACNS, primary angiitis of the central nervous system; CNS, central nervous system; cPACNS, childhood primary angiitis of the central nervous system; MRI, magnetic resonance imaging; NIHSS, National Institute of Health Stroke Scale; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CT, computed tomography; CSF, cerebrospinal fluid; CTA, computed tomography angiography; MCA, middle cerebral artery; DWI, diffusion weighted images; Fig., figure; IVIG, intravenous immunoglobulin; ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA antibodies; ANCAs, anti-neutrophil cytoplasmic antibodies; ENA, extractable nuclear antigen antibodies; anti-TPO, anti-thyroid peroxidase; HIV, human immunodeficiency virus; CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus; MRA, magnetic resonance angiography; IC, internal carotid; RSVS, reversible cerebral vasoconstriction syndrome; ACA, anterior cerebral artery; PCA, posterior cerebral artery

* Corresponding author at: Department of Neurology, Patras University Hospital, Patras 26504, Greece.

E-mail address: zmkefalopoulou@yahoo.com (Z.-M. Kefalopoulou).

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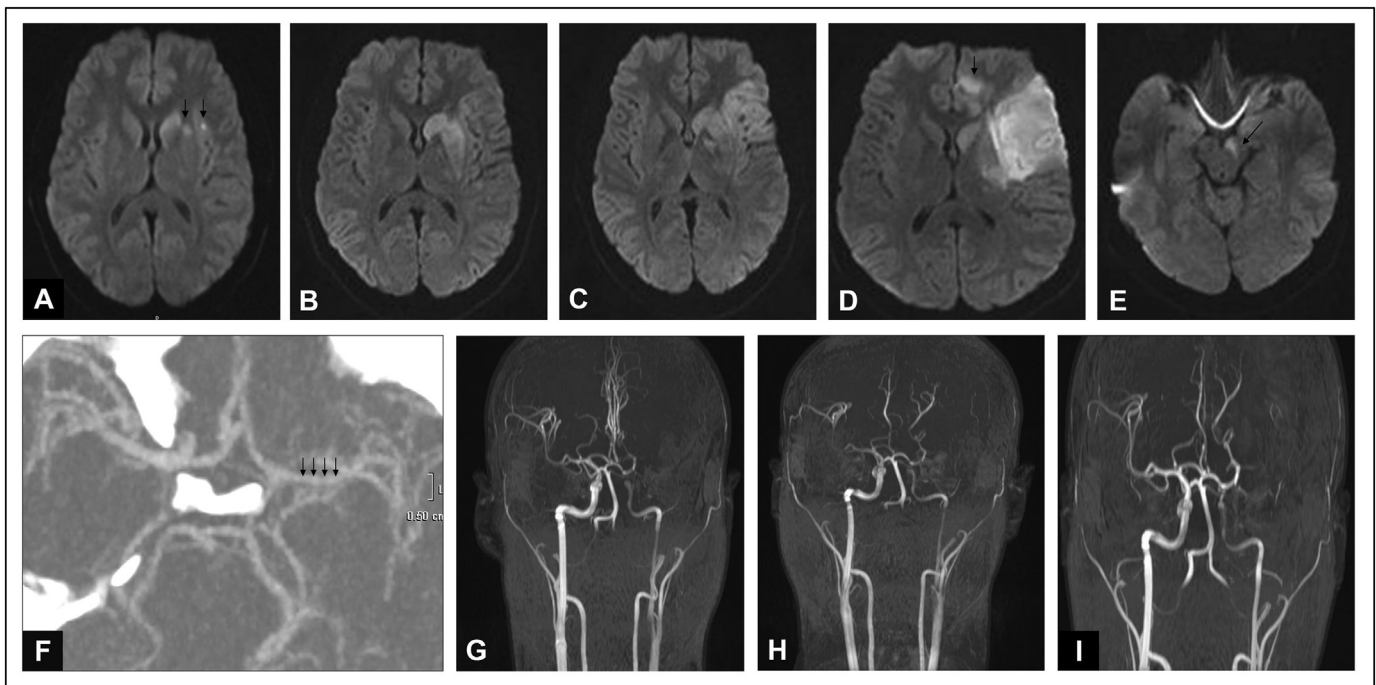


Fig. 1. Axial MRI DWI sequences demonstrating: (A) Acute ischemic punctate lesions (arrows) in the vascular distribution of left lenticulostriate arteries, branches of middle cerebral artery (MCA), at 24 h from symptom onset. (B) Larger areas of diffusion restriction in the left caudate, lentiform nuclei and of adjacent cortex, at 3 days follow-up. (C) Extended pathological signal in cortical and subcortical areas in the distribution of MCA, at 5 days follow-up. (D) Further radiological deterioration including additional ischemic areas in the distribution of left anterior cerebral artery (ACA) (arrow), and (E) left posterior cerebral artery (PCA) (arrow), at 10 days follow-up.

Angiographic findings: (F) Axial thick slab maximum intensity projection (reconstructed image) at the level of circle of Willis, showing relatively smaller diameter of the left M1 segment of MCA (arrows), compared to the contralateral side, at baseline. (G) Coronal plain MRA demonstrating marked stenosis of left internal carotid artery (ICA), in both extra- and intracranial segments and complete occlusion of left MCA, at 5 days follow up. (H) MRA showing more pronounced stenosis of left ICA, near complete occlusion of left ACA, stenosis of left PCA and left spinal arteries and evident involvement of right hemispheric vasculature, including right ICA, MCA, ACA, at 10 days follow-up. (I) MRA showing improved flow through ICA, MCA, ACA bilaterally, at 1-month follow-up. (MRI: magnetic resonance imaging; DWI: diffusion weighted images; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery; MRA: magnetic resonance angiography; ICA: internal carotid artery)

neutrophilia shift and a mildly elevated C-reactive protein (CRP), with normal erythrocyte sedimentation rate (ESR). Brain CT and carotid CT angiography (CTA) were normal, while brain CTA showed a mild stenosis of the left middle cerebral artery (MCA). Lumbar puncture revealed normal CSF cell count and cytology, glucose, and protein levels. Cardiological assessment, including transthoracic echocardiography, showed no abnormalities. An ischemic cerebral stroke was primarily suspected [National Institute of Health Stroke Scale (NIHSS) score: 7], while CNS infection could not be excluded. The patient was admitted in the Neurology Department, initially covered with both antithrombotic and anti-viral/antibiotic therapy.

A brain MRI within 24 h of symptom onset demonstrated subtle T2/Flair hyperintensities involving the left caudate, putamen and insular cortex, with restriction in diffusion weighted images (DWI), compatible with acute ischemic infarcts (Fig. 1A). Electroencephalography was unrevealing. Thorough endocrinology and thrombophilia panels (protein C, protein S, antithrombin III, common thrombophilia mutations, anticardiolipin antibodies, anti-beta2-glycoprotein, and lupus anticoagulant assays), as well as a peripheral blood smear evaluation were normal. Further cardiological investigations with transoesophageal echocardiography and 24-hour cardiac telemetry showed no irregularities. Diagnostic considerations at this stage included inflammatory/autoimmune aetiologies and the patient was initiated on intravenous immunoglobulin (IVIG), pending infectious workup. Testing for serum autoantibodies such as ANA, anti-dsDNA, ANCAs, ENA and anti-TPO was negative, with normal C3 and C4. Extensive laboratory investigations in blood and CSF (hepatitis, HIV, brucella, syphilis, borrelia, tuberculosis, CMV, HSV, VZV, West Nile, respiratory and enteroviruses panels,

cryptococcus, toxoplasmosis, fungi and parasites) failed to identify any infectious causative factors. Hence, corticosteroids were added on the 5th day from onset, 1 g of IV methylprednisolone for 5 days, followed by IV prednisone. Antibiotics were gradually withdrawn. CSF autoimmune encephalitis panel was also unremarkable.

Throughout the first 2 weeks of symptom initiation the patient exhibited continuous clinical deterioration with worsening of right-sided weakness (2+/5) and aphasia, brainstem signs and lethargy (NIHSS score: 15), despite ongoing treatment with steroids. Accordingly, repeat MRIs revealed a “spreading” of ischemic lesions in different vascular territories (Fig. 1B–E). Concomitant MRAs, using time of flight (TOF) technique, showed narrowing in the left internal carotid (IC), and flow absence of the left MCA and its branches (Fig. 1G). Repeat tests revealed progression of stenotic and occlusive lesions (Fig. 1H). The right-sided hemichorea has gradually waned within the first week from onset. Full body CT/CTA revealed no systemic abnormalities in keeping with absence of clinical or other laboratory manifestations from other systems. Nerve conduction studies were also normal. PACNS was thus considered the cardinal diagnosis. Given the poor response to steroids, the patient was initiated on immunosuppressive therapy with pulse cyclophosphamide (1gr IV). Three weeks after presentation the patient began to clinically stabilize. Follow-up MRA at 1 month demonstrated partial attenuation of vascular stenoses (Fig. 1I), in the absence of new parenchymal ischemic lesions. Besides prednisone taper, the patient received 6 cycles of cyclophosphamide (monthly infusions), and maintenance therapy with azathioprine thereafter. Meanwhile, he underwent intensive physiotherapy and speech therapy at the rehabilitation department. There was residual right spastic hemiparesis and

severe speech difficulty mainly due to the large left MCA infarct (NIHSS: 9, Modified Ranking scale: 3). Repeat imaging at 3, and 8 months revealed the pre-existing ischemic lesions, while there was no evidence of new vasculopathic changes.

3. Discussion

Childhood PACNS has become an important consideration in the workup of vascular strokes in children (Cantez and Benseler, 2008). Adopting the Calabrese and Mallek criteria proposed for adults, the diagnosis of cPACNS requires clinical evidence of a newly acquired neurological or psychiatric deficit, angiographic or histopathological features of CNS vasculitis, in the absence of an underlying systemic condition (Calabrese and Mallek, 1988; Benseler et al., 2006). Two distinct entities are currently recognized in the spectrum of cPACNS: angiography-positive cPACNS, affecting large- and medium-sized cerebral vessels (Benseler et al., 2006), and angiography-negative cPACNS, involving small-sized cerebral vessels (Benseler et al., 2005). The exact mechanisms that drive the inflammatory response causing endothelial injury remain unknown. Treatment of cPACNS consists of combinations of antithrombotic therapy, corticosteroids and other immunosuppressant agents depending on the underlying subtype. Given the rarity of the disorder, these protocols are mainly based on observational data rather than double-blind studies (Cellucci and Benseler, 2010).

Our patient presented with clinical and imaging (MRI/CTA) findings compatible with an acute cerebral infarct, involving a single vascular territory (Fig. 1A,F). The concomitant involuntary movements were consistent with basal ganglia as the primary area of ischemic insult. Movement disorders represent an uncommon but well documented complication of stroke, while hemichorea is systematically reported as the most frequent manifestation in the acute phase. In accordance with the literature, these movements have spontaneously waned within the first week from onset, a phenomenon possibly explained by brain plasticity. (Mehanna and Jankovic, 2013).

According to initial angiography via CTA, a left MCA pathology was revealed, while other intracranial arterial segments appeared normal (Fig. 1F). As soon as cardioembolic and hypercoagulable causes were ruled out, a vasculitic process affecting large/medium size vessels was highly suspected. Varicella-associated angiopathy, a common cause of stroke in children, which typically affects the M1 segment of MCA with subsequent basal ganglia infarcts, was highly considered. Other infectious or post-infectious states, systemic rheumatic conditions, moyamoya syndrome, as well as malignancies (especially lymphoma), were also contemplated. While CTA at presentation has revealed a benign pattern of stenosis (ie smooth, concentric and single), follow-up MRA showed an aggressive-appearing or “classic” configuration, with stenotic and occlusive pathology in multiple vascular beds (Aviv et al., 2007). Whether baseline angiography has underestimated a more widespread vascular involvement in our patient remains unknown. Conventional catheter angiography perhaps represents a superior technique and has long been considered the cornerstone in detecting luminal abnormalities, such as segmental narrowing (“beading”) or multi-locular occlusions, ‘typical’ of CNS vasculitis. However, it is usually unavailable on urgent grounds and carries risks of permanent complications. Hence, in the diagnostic process of CNS vasculitis, particularly in childhood, CTA/MRA remain the preferable approaches. (Aviv et al., 2007; Twilt and Benseler, 2012). Emerging non-invasive techniques such as high-resolution contrast-enhanced MRI hold significant promise in distinguishing the various causes of cerebral arteriopathies. However, the evidence to determine their precise value in early diagnosis of childhood CNS vasculitis is anticipated (Küker et al., 2008).

In our case, CSF analysis was also unrevealing, in keeping with findings from cPACNS series, where less than 50% of children with the angiography positive subtype are found with raised protein or

pleocytosis on CSF (Cellucci and Benseler, 2010). Further exhaustive investigations failed to identify a secondary cause of vasculitis in our patient, including numerous infections and autoimmune systemic conditions. There were no thunderclap headaches, no history of exposure to vasoactive substances, or any other precipitants to support the presence of reversible cerebral vasoconstriction syndrome (RCVS). Other non-inflammatory vasculopathies were not substantiated, and thus the diagnosis of idiopathic CNS vasculitis was made. Performing a risky procedure such as brain biopsy, in a patient already in critical condition, to further establish the diagnosis was considered unnecessary. According to suggested algorithms in paediatric age groups, diagnosis strongly depends on neuroimaging features, while brain biopsy is reserved for the angiography negative, small-vessel subtype of the disorder (Twilt and Benseler, 2012).

Our patient has shown an unusual course of relentless progression over the first 15 days, despite initiation of immunosuppressive treatment. Although there is no unanimous pattern of progression and treatment responsiveness of PACNS, it is mostly considered as a sub-acute evolving disorder rather than a fulminant condition. Reports of adult PACNS have recognized a small subset of patients (8–11%) with a catastrophic form of the disease, while those with rapid progression within 10 days are even less (Salvarani et al., 2011; Spence et al., 2019). In children, angiography positive PACNS has been traditionally divided into non-progressive and progressive subtypes, depending on the involvement of new vascular territories 3 months after initial angiography (Benseler et al., 2006). However, cases of rapid progression within this timeframe, have been rarely documented (Gallagher et al., 2001). Our patient's initial presentation, with acute onset of focal deficit due to lenticulostriate infarction, normal CSF and no headaches or other diffuse neurological signs, would best portray a case of non-progressive cPACNS. This phenotype typically involves unilateral stenosis of the distal ICA or proximal MCA, and tends to be a monophasic, self-limited condition (Cellucci et al., 2012; Elbers et al., 2016). Nevertheless, his clinical picture has deteriorated in a day by day basis, following successive ischemic events, as portrayed by serial MRI and angiographic images (Fig. 1).

Induction therapy with IV corticosteroids, withheld for a few days to exclude crucial infectious and malignant causes, failed to impede disease progression. Therefore, IV cyclophosphamide has been added following the protocol for progressive cPACNS (Cellucci and Benseler, 2010). Disease control was achieved one month after symptoms onset, however, the patient has suffered irreversible parenchymal damage and remained with significant neurological deficits due to initial strokes.

4. Conclusion

We present here a rare case of childhood PACNS with rapid progression resulting in recurrent strokes, within a short-time period. Our case highlights the complexities in management of this condition in the actual clinical setting, where early features are unspecific, and confirmation of diagnosis requires rigorous exclusion of many diverse disorders. Increased clinical suspicion, and structured rapid diagnostic protocols are therefore crucial, since favourable prognosis relies on instant initiation of aggressive immunosuppressive treatments.

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Declaration of Competing Interest

None.

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