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Case Report

Normal Brain MRI in an Adolescent with Primary Angiitis of the Central Nervous System: A Case Report. The Challenge of Diagnosing PACNS

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1. Abstract

We report on an adolescent affected by a progressive primary angiitis of the central nervous system (PACNS) and constantly normal high-resolution brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) exam.

A 15-years-old-male came to our attention for a severe diffuse headache, associated with recurrent episodes of vomiting, consciousness impairment and spatial-temporal disorientation. High-resolution brain magnetic resonance imaging (MRIs) and cerebrospinal fluid (CSF) were constantly normal despite the severity of symptoms and the evidence of multiple progressive focal stenoses in anterior and posterior circulations as documented by magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) exams. Based on angiographic features, the evidence of progressive vascular stenoses, neurological symptoms and their improvement under steroid treatment, a diagnosis of PACNS was made, thus excluding a reversible cerebral vasoconstriction syndrome. Mycophenolate mofetil was started and MRA detected a progressive improvement over the following 12 months.

Anecdotal PACNS cases with normal brain MRI have been reported in adulthood and they have been related to technical limitations and poor quality images, thus normal MRI combined with normal CSF exam, is considered a criterion of exclusion for PACNS. We believe that MRA should always be performed in individuals with neurological symptoms even with normal brain MRI and a diagnosis of a progressive vasculitis should be suspected in the absence of any other possible alternative diagnoses. In our case MRA has been helpful in assessing abnormalities confirmed by DSA and monitoring the disease.

2. Keywords

Primary Angiitis of the Central Nervous System; Magnetic Resonance Imaging; Magnetic Resonance Angiography; Digital Cerebral Angiography; Case Report

3. Introduction

Primary angiitis of the central nervous system (PACNS) is a potentially severe inflammatory disease of unknown origin confined to the cerebral vessels [1-4]. The symptoms of PACNS at the onset are varied and unspecific and often insidious. Headache, cognitive deficits, seizures and focal neurological symptoms are most commonly observed. Early clinical recognition and a prompt appropriate treatment are necessary to reduce morbidity and mortality. Diagnosis is extremely hampered by the broad and unspecific symptomatology and by the low specificity of the diagnostic approaches. Reversible cerebral vasoconstriction syndrome (RCVS) is a non-inflammatory non-atheromatous self-limited vasculopathy to be considered in the differential diagnosis of PACNS [5]. Patients with PACNS often show abnormal brain magnetic resonance imaging (MRI) [6]. Typical changes include multiple focal white and grey matter lesions, contrast medium enhanced parenchymal lesions, leptomeningeal enhancement, parenchymal haemorrhages as well as microbleeds. Less commonly and usually in the adult population, tumor-like mass lesions and a generalized atrophy have been reported [6]. Arterial wall thickening and enhancement of vessel walls have been added as useful pattern for the diagnosis of vasculitis [7]. The current gold standard for vessel imaging in PACNS is Digital Subtraction Angiography (DSA) which has an overall sensitivity varying between 40 and 90%. Brain biopsy is the

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only eligible technique to establish a definite diagnosis of PACNS, however, due to its invasive nature and false negative occurrence, it is rarely performed in children [8]. While MRI alone cannot make the diagnosis, it is important to note that a normal MRI, combined with normal cerebrospinal fluid (CSF) exam, is considered a criterion of exclusion for the diagnosis of PACNS [3,4]. It has been reported that MRI can detect abnormalities in more than 98% of children with PACNS and anecdotal cases with normal MRI examination have been considered as due to technical limitations [9]. Here we report on an adolescent affected by PACNS with constantly normal high-resolution brain MRIs.

4. Case Presentation

A 15-year-old boy, with a history of sporadic episodes of a mild frontal cephalalgia since the age of 8 years was referred to Meyer Children's Hospital for a severe diffuse headache arisen about 10 days earlier. Headache was initially mild and intermittent and became severe and persistent over time with associated recurrent episodes of vomiting. Neurological examination revealed consciousness impairment and spatial-temporal disorientation. Neither focal neurological deficits nor dysarthria and ataxia were observed. General clinical conditions were good except for high blood pressure (100/165 mmHg) that required therapy for the following 3 weeks until normalization. Blood and urinary exams were normal. Infectious diseases testing for HSV1, HSV2, VZV, EBV, CMV, HBV, HCV, Borrelia Burgdorferi, Rickettsia, Treponema pallidum were also negative. Cerebrospinal fluid analysis, including the IgG index and oligoclonal bands, was normal. In the suspicion of encephalitis, broad spectrum antibiotic therapy, acyclovir and low dose of steroids were administered with no clinical improvement. A computerized tomography (CT) scan of the brain was normal. No cerebral infarctions were observed on MRI with conventional sequences (including T13D FFE before and after contrast, axial and coronal T2 TSE, axial 2DFLAIR, FLAIR VISTA and DWI images) (Figure 1A), while magnetic resonance angiography (MRA) (time-of-flight MR angiography of the circle of Willis) highlighted multiple focal narrowing of the anterior and posterior circulation (Figure 2A, D, G). No arterial walls enhancement was detected after injection of contrast media. Cerebral DSA showed multiple focal stenoses of the cortical segments of two branches of the left middle cerebral artery and pericallosal arteries (Figure 2B, E) and of the cortical segments of the posterior cerebral and superior cerebellar arteries (Figure 2H, L), thus confirming the suspicion of cerebral vasculitis. Medical treatment with high doses of intravenous corticosteroids and acetylsalicylic acid was started. In the following 2 weeks, a complete normalization of the neurological status was observed. Patient remained asymptomatic even after steroid withdrawal. A 3Tesla (3T) brain MRI performed 4 months after the onset of symptoms remained normal (Figure 1B). On MRA an evident regression of most of the previously documented stenoses in the anterior circulation was observed, while additional multiple focal stenoses in the posterior circulation appeared. Thus a second DSA was performed after 5 weeks confirming the regression of stenosis in the anterior circulation (Figure 2C, F) and worsening of the disease in the posterior circulation (Figure 2M). After the exclusion of any other medical condition associated to secondary vasculitis, a diagnosis of progressive primary cerebral vasculitis of the CNS was made [1-5,10-12]. Mycophenolate mofetil (MMF) was started as immunosuppressive therapy of a PACNS and progressively increased according to an approved protocol in use at our hospital [13]. Control MRA was performed every 6 months. A gradual improvement of MRA was observed and became normal at one year. MMF was withdrawn at three years. At the latest follow-up, 4 years after clinical presentation and one year after drug withdrawal, control brain MRI and MRA are still normal (Figure 2I).

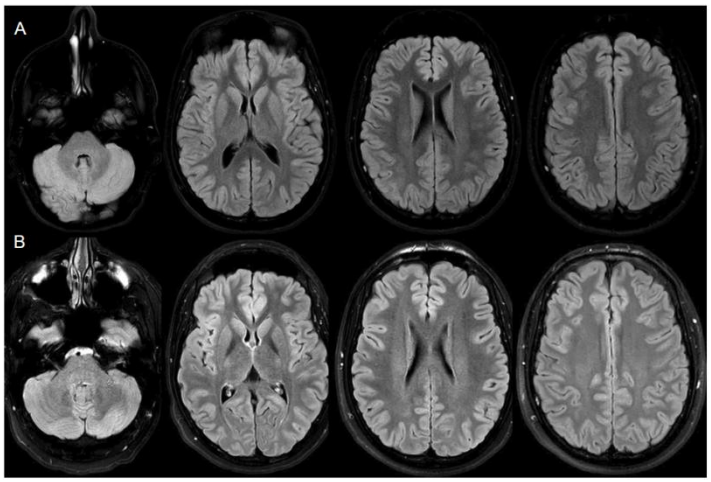

Figure 1: Comparison between the MRIs performed at the hospitalization (A) and after 4 months (B): FLAIR images show persistent absence of abnormalities.

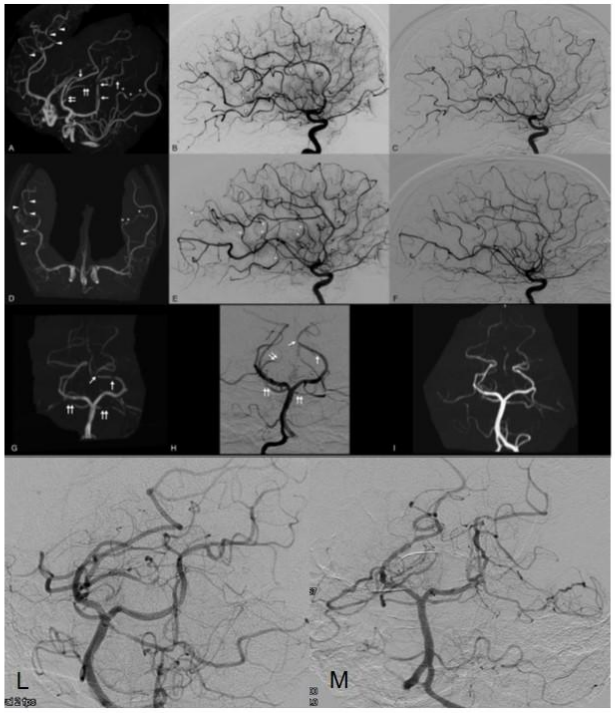

Figure 2: Comparison between the 3D reconstructions of the first MRA in anterior left oblique projection of the anterior and posterior cerebral arterial circulation (A) and cranio-caudal projection of the anterior cerebral circulation (D); the lateral projections of right (B) and left (E) internal carotid arteries at the first cerebral DSA done one week after the MRA; and the lateral projections of right (C) and left (F) internal carotid arteries at the control cerebral DSA done 4 months after the first one. Multiple focal stenoses are visible in the MRA (A and D) and in the first DSA (B and E) in the cortical segments of the branches of the posterior cerebral arteries (white arrows), of the superior cerebellar arteries (double white arrows), of the right (white arrowheads) and left (white asterisks) middle cerebral arteries, and of the right (black arrowhead) and left (black asterisks) anterior cerebral arteries. The stenoses are no more evident in the arteries of the anterior circulation after 4 months (C and F).
In the bottom comparison between the 3D reconstructions of the MRA in antero-posterior projection of the posterior cerebral arterial circulation (G); the postero-anterior (H) projection of the arteries of the posterior circulation at the first cerebral DSA done one week after the MRA; and the 3D reconstructions of the MRA in antero-posterior projection of the posterior cerebral arterial circulation (I) done 4 months after the first one. Multiple focal stenoses are visible in the MRA (G) and in the first DSA (H) in the cortical segments of the branches of the posterior cerebral arteries (white arrows), of the superior cerebellar arteries (double white arrows). At the last follow up MRA (I) the stenosis are no more evident. A caudal fenestration of the basilar artery is present as anatomical variant. Comparison between postero-anterior projection of the arteries of the posterior circulation at the first cerebral DSA (L) and the second DSA performed after 5months (M): a progression of the disease is documented by the more evident stenoses.

5. Discussion and Conclusions

We report the case of an adolescent with a documented progressive PACNS and normal MRI and CSF exam. Diagnosis of PACNS is a combination of clinical, imaging and laboratory parameters [1-4]. In our patient we have diagnosed a probable PACNS excluding an RCVS although these pathologies have similar clinical presentation based on the abnormalities of cerebral arteries found at MRA and DSA. In our case the abnormalities are more like the typical irregular notched appearance in the PACNS, rather than the widespread "sausage-on-a-string" appearance in the RCVS [10,14]. Furthermore their progression in the first year, the clinical improvement during high-dose steroid therapy and the MMF efficacy in stopping disease progression correlate more likely with a PACNS instead of a RCVS [14,15]. Brain MRI remained normal during the 3 years' follow-up and cerebral infarctions were never observed despite evidence of vascular progressive involvement. It has been reported that MRI can detect abnormalities in more than 98% of children with PACNS and anecdotal cases with normal MRI examination have been considered as due to technical limitations [9]. Our patient performed the MRIs in a 3 Tesla scanner, so that a missed detection of parenchymal brain lesions due to a technical limitation is unlikely. In some cases of PACNS, the arteries involved are very small (SV-PACNS) so the detection of abnormalities could be beyond the resolution of current angiographic techniques. High resolution MRI allow to detect sign of walls inflammation (thickening and enhancement) [7,10]. In our case the majority of the vessels affected are small and this could partially explain why the thickening of vessels walls and their enhancement were not detected.

Brain biopsy is the gold standard but is an invasive procedure that can lead to false-negative results. Since the patient improved with the therapy we decided not to perform the biopsy.

From our case a few considerations can be made: 1) an MRI without abnormalities does not rule out a diagnosis of PACNS; 2) MRA is mandatory in a diagnostic work-up in the suspicion of vasculitis, even in the absence of abnormalities on a conventional MRI; 3) DSA is the gold standard for confirming the diagnosis of vasculitis but MRA can be used to monitor the disease; 4) other sequences must be used in the suspicion of vasculitis such as Susceptibility Weighted Imaging (SWI), T1 3D with contrast media and eventually black-blood MRI, useful for the study of vessel walls.

Certainly a strong communication between the neurologist and the neuro-radiologist is advisable in order to perform a correct diagnostic planning for patients with unspecific neurological symptoms in which a diagnosis of vasculitis should always be suspected even in angiography-negative or normal MRI. Well-designed studies are obviously necessary to better understand clinical and radiological wide spectrum of PACNS and in particular to better characterize those individuals with normal brain high-resolution MRI.

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