Archives of Pediatrics
Bossi G, et al. Arch Pediatr 7: 199.
www.doi.org/10.29011/2575-825X.100099
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Case Report

Pseudotumoral Acute Hemicerebellitis Due to Parvovirus B19 Infection in a Child: Diagnostic Pitfalls, Successful Treatment with Intravenous Immunoglobulins and Long-Term Follow-Up

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Citation: Bossi G, Mussati G, Fiorito I, Vanzù G, Marseglia GL (2022) Pseudotumoral Acute Hemicerebellitis Due to Parvovirus B19 Infection in a Child: Diagnostic Pitfalls, Successful Treatment with Intravenous Immunoglobulins and Long-Term Follow-Up. Arch Pediatr 7: 199. DOI: 10.29011/2575-825X.100099

Received Date: 28 January, 2022; **Accepted Date:** 01 February, 2022; **Published Date:** 04 February 2022

Abstract

Pseudotumoral Acute Hemicerebellitis is a very rare disease of childhood, resulting from the acute inflammation of a single cerebellar hemisphere. The clinical presentation and the neuroradiological findings strictly resembles those of posterior fossa tumors. It is regarded as a para-infectious disorder, mainly related to viral infections, albeit in almost all cases reported in the literature, the cause-effect relationship between a specific virus and this peculiar condition only relied on the recent medical history of the patient or on plasma serological tests. Molecular assays, such as Polymerase Chain Reaction has never been applied to cerebro-spinal fluid to identify the infectious agent with certainty, and among all the viruses implied, Parvovirus B19 has never been reported in the literature. Pseudotumoral Acute Hemicerebellitis requires prompt and proper medical treatment, in order to avoid the possible complications of raised intracranial pressure. Different combinations of antimicrobial agents, steroids and mannitol have been used as empirical therapy, but a very few cases of successful treatment with intravenous immunoglobulins have been reported so far. Despite usually Pseudotumoral Acute Hemicerebellitis shows a good response to therapy and a benign course, with neurological complete recovery, residual cerebellar gliosis and atrophy have been described shortly after the disease onset. Nevertheless, in all the cases reported in the literature, the clinical and neuroradiological follow-up is too short to demonstrate the long-term radiological sequelae and to establish the clinical relevance of the residual cerebellar parenchymal damage. Hereby we describe clinical presentation, diagnosis, successful treatment and long-term clinical and neuroradiological follow-up of the first pediatric case of Pseudotumoral Acute Hemicerebellitis, definitely caused by Parvovirus B19, identified in the cerebro-spinal fluid by Polymerase Chain Reaction.

Keywords: Pseudotumoral; Hemicerebellitis; Children; Parvovirus B19; Intravenous immunoglobulins; Magnetic resonance imaging

Abbreviations: PVB19: Parvovirus B19; EEG: Electroencephalography; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; CSF: Cerebro-Spinal Fluid; PCR: Polymerase Chain Reaction; IVIG: Intravenous Immunoglobulins; NGS: Next-Generation Sequencing

Introduction

Acute Hemicerebellitis is a very uncommon pediatric disorder, probably of para-infectious origin, characterized by an unilateral cerebellar inflammatory process [1,2]. Pseudotumoral Acute Hemicerebellitis is an even rarer form of the disease, whose clinical and radiological features strictly resemble those of a posterior fossa tumor. It requires a careful differential diagnosis, together with a prompt and proper medical treatment, in order to avoid possible complications due to increased intracranial pressure [3-5]. Despite its benign course, residual cerebellar atrophy can be evident in up to 50% of cases. Nevertheless, all the patients reported in the literature had a clinical and radiological follow-up insufficient to establish the real long- term clinical relevance of the parenchymal damage [1]. Hereby we describe clinical presentation, diagnosis, successful treatment and long term follow-up of a child affected by Pseudotumoral Acute Hemicerebellitis, definitely caused by Parvovirus B19 (PVB19).

Case Report

A 8-year-old boy was admitted to our emergency room with a 1-week history of vomiting and worsening frontal headache, unresponsive to acetaminophen. No recent infections, vaccinations, toxic exposure, head injuries were reported. The child appeared suffering but fully oriented; his neurological examination was normal, except for slurred speech. Full blood count, biochemistry and inflammatory markers were normal. No papilledema was evident. Electroencephalography (EEG) showed isolated sharp waves, sometimes with right prominence, in the posterior region. The basal cranial Computed Tomography (CT) demonstrated a wide hypodense lesion in the left cerebellar hemisphere, with slight mass effect on the fourth ventricle, suspected for posterior fossa tumor. The Magnetic Resonance Imaging (MRI) showed a swollen left cerebellar hemisphere, with a high signal intensity in T2 weighted images, involving gray and white matter in the left cerebellar hemisphere; slight downwards displaced tonsils; supratentorial ventricular dilatation due to the 4th ventricle and silvian acqueduct obliteration, with minimal transependymal flow of Cerebro Spinal Fluid (CSF) around the ventricular trigones, mesial right cerebellar emisphere and partially the left tonsil. Post-gadolinium T1-weighted images revealed slight leptomeningeal enhancement and no signs of restricted diffusion (Figure 1). The CSF analysis showed pleocytosis (107 cells/uL, mononuclear predominance), slightly elevated protein (51 mg/dL; n.v. 15-45), glucose 49 mg/dl (n.v 50-80). Normal CSF citology and negative bio-markers (β-HCG and α-fetoprotein) ruled out malignancy. CSF and blood cultures were negative for bacteria, fungi and tuberculosis. Polymerase Chain Reaction (PCR) tested positive for PVB19 both in CSF (3.1×10^4 copies/mL) and blood (1.0×10^5 copies/mL), and negative for other viruses (Epstein Barr, Cytomegalovirus, Varicella-Zoster, Herpes simplex 1 and 2, Herpes 6 and 7, Enterovirus). Past recent PVB19 infection was confirmed by serology (positive specific IgG and IgM). Autoimmunity tests were negative. In suspicion of para-infectious hemicerebellitis, our patient was empirically treated with IVIG (2 g/Kg/day, 2 days); intravenous acyclovir plus ceftriaxone were discontinued soon after the negative results of cultures and viral tests. Symptoms improved promptly and the child was quickly discharged completely asymptomatic, with a normal EEG. Brain MRI was repeated at 2 and 6 months and showed progressive cerebellar cortical atrophy with compensatory sulci dilatation and dilated cisterna magna. After the disease onset, our patient has been followed with periodic clinical, radiologic and EEG assessments. The latest MRI, more than eight years later, confirms cerebellar cortical atrophy, hyperintense signal in the cerebellar hemispheres due to gliosis and ex-vacuo enlargement of the fourth ventricle (Figure 2). Even so, he is completely asymptomatic, and both his neurologic examination and functional neurocognitive tests are completely normal.

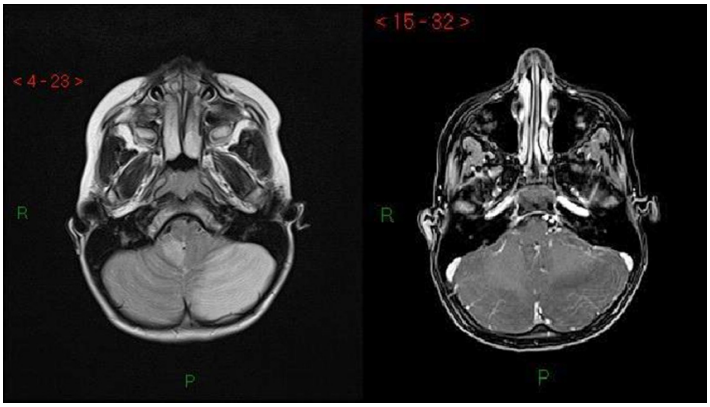

Figure 1: (A) Axial FLAIR MRI showing a swollen hyperintense left cerebellar hemisphere exerting mass effect on the fourth ventricle. (B) T2-weighted MRI showing cerebellar leptomeningeal enhancement.

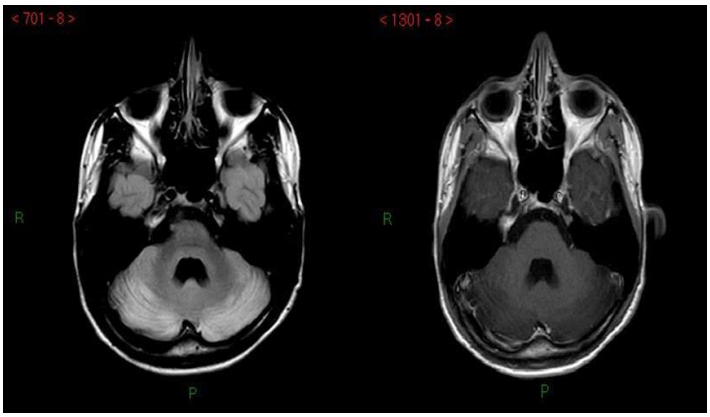

Figure 2: (A) Axial FLAIR MRI showing a cerebellar atrophy. (B) T2-weighted MRI showing the absence of cerebellar leptomeningeal enhancement.

Discussion

Acute hemicerebellitis is an uncommon form of pediatric cerebellitis, characterized by cerebellar unilateral involvement, probably as a result of impaired blood flow and/or anatomic variant of the posterior circulation system [2,6]. Pseudotumoral Acute Hemicerebellitis is an exceptionally rare variant of hemicerebellitis: from 1990 and 2019, only 36 pediatric cases have been reported [6]. Patients can present with cerebellar signs, signs of raised intracranial pressure or both, while its radiological presentation strictly resembles that of unilateral cerebellar tumor [6]. Due to the frequent temporal association between the symptoms onset and a previous infectious diseases, acute hemicerebellitis, including its pseudotumoral subtype, is considered as the consequence of a cerebellar inflammation of infectious or para-infectious origin. Nevertheless, in more than half of patients, the causative agent remains entirely unknown or, at most, is only suspected, according to the recent medical history [3-5]. A large number of viruses (Varicella-zoster, Epstein-Barr, Rotavirus, Mumps, Measles, Rubella, Influenza, Enterovirus) and some bacteria (Salmonella, Mycoplasma pn.) have been implicated but, in most cases, the cause-effect relationship between the putative infectious agent and hemicerebellitis relied only on serological tests applied to plasma or CSF. In only two patients the infective agent (*Coxiella burnetti*, Enterovirus) was isolated in the CSF. In none of the cases reported in the literature the PCR assay was applied to CSF [7,8]. MRI is currently the gold standard for the differential diagnosis, mainly with posterior fossa tumors and demyelinating disorders [4]. The radiological findings are typically those of a swollen cerebellar hemisphere, with hypointense signal on T1-weightened images and hyperintense signal on T2-weighted images, pial enhancement along the cerebellar folia in the post-gadolinium T1-weightened images, various degree of mass effect on the fourth ventricle up to hydrocephalus, tonsillar or transtentorial herniation [3,9]. Albeit it is regarded as a benign condition, Pseudotumoral Acute Hemicerebellitis requires prompt and proper medical treatment, in order to avoid the possible complications of raised intracranial pressure. Due to the possible infectious aetiology, empiric antimicrobial therapy (antivirals, antibiotics, antimycotics) should always be administered, sometimes in association with mannitol to decrease intracranial pressure. Corticosteroids may be helpful in shorten the time to recovery and in cases with severe symptoms of intracranial hypertension [1,6]. Successful therapy with IVIG and high dose steroids has been reported in a few cases resistant to first-line therapy [1]. Diagnostic surgery should be absolutely avoided, while ventricular drainage and/or decompressive surgery should be reserved only to the cases of severe obstructive hydrocephalus or brain stem compression. Uncomplicated Pseudotumoral Acute Hemicerebellitis shows a good response to medical therapy and a benign course, with complete neurological recovery. Nevertheless radiological changes, mainly gliosis and atrophy, can be evident at MRI soon after the disease onset [1,10]. We reported a case of Pseudotumoral Acute Hemicerebellitis definitely caused by Parvovirus B19, identified in CSF and plasma with PCR, that occurred in a previously healthy child, whose recent clinical history lacked the classic clinical features of this infection. While some definite clinical syndromes due to PVB19 are well known - erythema infectiousum, arthritis, hydrops fetalis, aplastic crisis and pure red cell aplasia in immunocompromised patients - the neurological disorders caused by this virus are poorly reported [11]. Only 34 children with PVB19 associated neurological manifestation have been described so far: acute encephalitis and encephalopathy were the most common features and a significant proportion of patients had underlying diseases or immunodeficiencies [12,13]. To the best of our knowledge, this is the first reported pediatric case of Pseudotumoral Acute Hemicerebellitis definitely associated with PVB19 infection, confirmed by PCR applied to CSF and plasma. Our patient was timely treated with IVIG as first-line therapy, together with empiric antibiotic and antiviral therapy, and he improved rapidly. Unlike all the patients affected by Pseudotumoral Acute Hemicerebellitis described so far, who had a very short MRI follow-up (0.5-32 months, median 2 months), our patient received long-term, periodic clinical and radiological assessment. The latest MRI, performed 8 years after the disease onset, shows mild hemispheric cerebellar atrophy with gliosis and ex-vacuo enlargement of the fourth ventricle. Nonetheless, the neurological examinationof our patient is totally normal, as well as his intellectual faculties.

Conclusion

Pseudotumoral Acute Hemicerebellitis is a very rare pediatric disorder, characterized by unilateral inflammation of the cerebellum. Because of its peculiar clinical presentation, with signs and symptoms of raised intracranial pressure, this condition

may mimic a posterior fossa tumor and deserves an accurate differential diagnosis. MRI is the gold standard for the diagnosis of this disease, which may remain undetected on CT or misdiagnosed as a posterior fossa tumor. There are no defined guidelines for the treatment of Pseudotumoral Acute Hemicerebellitis, but, due to its suspected para-infectious aetiology, empirical therapy with antibiotics and antiviral is strongly recommended. Mannitol can be required to reduce intracranial hypertension, while the real effect of steroids remains undefined. In our experience, IVIG proved to be a first-line treatment extraordinarily effective if timely administered, not to be reserved only to patients resistant to former therapies. Any case of Pseudotumoral Acute Hemicerebellitis deserves an accurate microbiologic diagnostic work-up with CSF examination. In particular, viruses should be actively investigated in CSF with molecular assays, PCR and, if possible, Next-Generation Sequencing (NGS) [14]. As our experience testifies, paediatricians need to be aware of the role of PVB19 as potential causative agent of hemicerebellitis, even when the recent medical history of the patient lacks of the characteristic features of this infection. Due the reported possibility of false negative results of PCR, high-throughput sequencing technique, as metagenomics-based NGS, could be considered in order to enhance the chance to detect PVB19 in CSF [15]. The definite diagnosis of Pseudotumoral Acute Hemicerebellitis associated to PVB19 infection is crucial, as far as it might benefit from an early IVIG treatment. Long-term radiological sequelae are frequent and persistent, so that patients with a past history of Pseudotumoral Acute Hemicerebellitis deserve a properly extended clinical follow-up in order to detect possible neuro-cognitive deficit.

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