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CASE REPORT

Kinsbourne syndrome as a differential diagnosis of encephalitis: a case report

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Abstract

Opsoclonus-myoclonus-ataxia syndrome, or Kinsbourne syndrome, is characterized by involuntary, abrupt, conjugate, multidirectional eye movements, often associated with postural tremors, cerebellar ataxia, encephalopathy, and behavioral disorders. Its diagnosis is made based on the presence of at least 3 of these clinical features: (1) opsoclonus; (2) myoclonus or ataxia; (3) sleep disorder; (4) neuroblastoma. Due to its rarity and limited awareness among healthcare professionals, it can be confused with viral encephalitis and acute cerebellar ataxia, which seems to cause a prolonged time interval between the onset of symptoms and appropriate therapy. Given its intrinsic relationship with occult neuroblastoma, this article aims to describe a case of Kinsbourne syndrome with a viral prodrome and occult neoplasia, initially managed as viral encephalitis. Once the diagnosis was established, treatment consisted of corticosteroid therapy, intravenous immunoglobulin infusion, and tumor excision with good clinical outcomes.

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INTRODUCTION

Opsoclonus-myooclonus-ataxia syndrome (OMAS), or Kinsbourne syndrome, is characterized by involuntary, conjugate, multidirectional eye movements, which are often associated with postural tremors, cerebellar ataxia, encephalopathy, and behavioral disorders.¹ It is a rare syndrome, with an estimated incidence of 0.18 per million each year, with an average age of presentation at 18 months and no difference between sexes.²

This syndrome's etiology has not yet been completely elucidated in the literature, however, evidence suggests that it is an immune-mediated disorder. Furthermore, more than half of cases are associated with a later diagnosis of neuroblastoma, although only about 2 to 3% of children with this type of tumor will present this condition.³ Other possible etiologies are idiopathic or post-infectious, as secondary to streptococcus or varicella-zoster.¹

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Given that it is not widespread among healthcare professionals, the time interval between the onset of symptoms and the establishment of appropriate therapy is often prolonged, ranging from 1 week to 30 months, according to Mitchell et al, with a median of 4 months.⁴ Koh et al suggest that this time is 2 to 12 weeks, while for Pohl et al it is approximately 10.9 weeks.^{5,6}

This diagnostic delay seems to be multifactorial and, as this condition frequently presents viral prodromes, it can be confused with viral encephalitis and acute cerebellar ataxia. Therefore in those clinical settings, Kinsbourne syndrome is a relevant differential diagnosis that must be listed, especially for its intrinsic relationship with occult neuroblastoma.⁷

Thus, the present study aims to report a case of Kinsbourne Syndrome initially diagnosed and treated as viral encephalitis.

CASE REPORT

We report a case of an infant who was seen in a philanthropic children's Hospital in Salvador, Bahia.

A female infant, 01-year-old, previously healthy, started fever, prostration, and vomiting, which evolved with difficulty walking. During the first hospitalization, she was diagnosed with viral encephalitis and treated with acyclovir for 21 days, during which the patient developed tremors, opsoclonus eye movements, and irritability. A cerebrospinal fluid analysis and head tomography were performed, and the results were normal.

Six days after discharge, she sought medical attention again due to a new case of vomiting and the persistence of cerebellar ataxia. A new cerebrospinal fluid analysis, head magnetic resonance imaging, and abdominal ultrasound were

performed, showing no changes. The child was released after stabilization of vomiting. Myoclonus, opsoclonus, and ataxia symptoms were interpreted as sequelae of encephalitis and they persisted after discharge.

After 6 months, in an outpatient consultation with a neurologist, she was first diagnosed with Kinsbourne Syndrome. Screening for neuroblastoma was carried out, which was negative, and pulse therapy and infusion of human immunoglobulin (0.5g/kg/dose) were therefore started, with complete regression of neurological symptoms. One month later, in an attempt to wean from corticosteroid therapy, she presented a recurrence of previous symptoms, associated with sleep disturbance. In this scenario, new screening tests were carried out which showed an expansive right lumbar paravertebral formation.

After re-establishing a full dose of corticosteroids, tumor resection was indicated, which was performed without complications. The anatomopathological analysis resulted in a mature ganglioneuroma, a benign and rare tumor.

The patient progressed with total regression of neurological symptoms and is being weaned from corticosteroid therapy with good tolerance.

This project was approved by our institution's Research Ethics Committee (CAAE 80512124.1.0000.5543, number 6.920.333). The case report was authorized by the patient's parents through the signing of the free and informed consent form.

DISCUSSION

We reported a case of an infant diagnosed with Kinsbourne syndrome that presented viral prodromes and occult neoplasia, and that was initially conducted as viral encephalitis. Once the diagnosis was established, treatment consisted of corticosteroid therapy, intravenous immunoglobulin infusion, and tumor excision, with good clinical outcomes, revealing a rare type of benign tumor as the underlying cause of OMAS.

As we have discussed in the first place, the diagnosis of OMAS is established if at least three of the following features are present: (1) opsoclonus; (2) myoclonus or ataxia; (3) sleep disorder; (4) neuroblastoma; but its classical presentation is marked by the triad: opsoclonus, myoclonus and ataxia - which was the key to the diagnosis of our patient.

The association between Kinsbourne syndrome and neuroblastic tumors such as neuroblastoma and ganglioneuroma has been studied in the past decades. Even though solid tumors are often the underlying cause of the syndrome, viral infections seem to play an important role as triggers to the onset of symptoms.⁸ We noticed that this pattern was followed by our patient, who was previously healthy and, after developing what seemed to be viral symptoms as fever, vomiting and prostration, evolved with neurological findings compatible with OMAS.

It is well established in the literature that every patient with opsoclonus must undergo appropriate evaluation, which includes neuroimaging of the entire neural-axis with contrast and a lumbar puncture, as well as excluding other underlying causes such as intoxication, infections and metabolic disorders.⁹ Whether early investigation results negative, re-evaluation in order to exclude hidden tumors must be performed.¹⁰ Particularly, this was the clinical setting of our patient, that was evaluated twice with laboratory tests, cerebrospinal fluid analysis and neuroimaging before any alteration was found 06 months later. In the other hand, it is possible that even after extensive investigation no occult neoplasm is found, thus resulting in idiopathic OMAS, as described by Rosse et al who reported an infant successfully treated with corticosteroid therapy, IVIG and rituximab.¹¹

And as we know that half of OMAS cases may be associated with neuroblastoma, serum and urine assessment of catecholamines [homovanillic acid (HVA) and vanillylmandelic acid (VMA)] is recommended, in addition to inflammatory markers such as C-reactive protein and ferritin, and tumor lysis syndrome tests (lactate dehydrogenase and electrolytes).¹²

In this scenario, a retrospective single-center study that followed 13 children with OMAS proposed a diagnostic algorithm for clinically suspected OMAS. They proposed that the initial investigation should include blood testing (with thyroid, liver, autoimmune, and metabolic profiles, as well as alpha-fetoprotein, viral Polymerase Chain Reactions, toxicology, and vitamin levels), electroencephalogram, urinalysis (toxicology and organic acid chromatography), cranial MRI, and ophthalmological evaluation. If diagnostic uncertainty persists, cerebrospinal fluid collection should be performed, and if an infection is suspected, serology should be performed. If anatomical abnormalities are identified on MRI, neoplasia screening should be performed with testicular, cervical, abdominal, and pelvic ultrasound. Finally, if the initial screening is normal, total body MRI and/or PET scan and/or scintigraphy should be performed, and if symptoms are progressive, genetic sequencing should be performed.¹³

When we compare our findings with the literature, we observed that in a 10-year cohort of children followed in the neurology department of the largest pediatric hospital in Latin America, out of a universe of 50,000 patients analyzed, 10 were diagnosed with OMAS. Of the sample studied, half had neoplasia as the underlying cause of Kinsbourne syndrome, such as neuroblastoma, Burkitt's lymphoma, and leukemia. Only 1 patient showed complete recovery of symptoms after treatment.¹⁴ Our patient, on the other hand, had a benign neuroblastic tumor as the primary cause of the syndrome and after immunosuppressive treatment associated with tumor excision, she evolved with complete resolution of symptoms.

Also, in a Japanese cohort of 73 patients with OMAS, the time interval between the onset of OMAS and initial therapy establishment ranged from 3 to 76 days, within a mean of 20 days. In addition, they observed that children with

neurological sequelae tended to have a prolonged time interval between the onset of symptoms and appropriate therapy, suggesting that early diagnosis might improve neurological outcomes.¹⁵ Paralelly, in an Indian cohort, the mean interval was 6 months (range: 2-24 months) - which coincides with our patient's time gap between onset of symptoms and correct diagnosis.¹⁶ This delay in diagnosis can be attributed to first misdiagnosis - as we experienced with our patient -, and to atypical presentation of symptoms.^{15,16}

This way, the key to a timely and precise diagnosis seems to require special attention to the overlap of three clinical entities: acute cerebellar ataxia, acute cerebellitis and opsoclonus-myoclonus syndrome. While acute cerebellar ataxia is a benign condition, marked by ataxia, nystagmus, hypotonia and dysarthria, cerebellitis is a more severe clinical setting with focal neurological signs, high intracranial pressure and alteration of consciousness.¹⁷ In the first, neuroimaging is normal, prognosis is good and a faster recovery is expected, while in cerebellitis, neuroimaging is abnormal, symptoms can be fulminant and long-term outcomes are less favorable.^{18,19} Although ataxia is seen in all three settings, the presence of persistent ataxia accompanied by behavioral symptoms and action-induced myoclonus should make clinicians think about OMAS.²⁰

In this scenario, once the diagnosis is established, proper therapy must be indicated. Despite the fact that there are still a lack of clinical trials in this area, for its possible immune-mediated nature, immunotherapy is widespread. In a Spanish cohort of 20 patients with OMAS who were treated with tritherapy - immunoglobulin infusion (IVIG), dexamethasone and second line drug as rituximab or ciclosporin -, although statically association between early onset of therapy and better prognosis wasn't find, a lower prevalence of cognitive sequelae was seen at 02 years.²⁰ Likewise, an open-label clinical trial randomized 53 children with neuroblastic malign tumors to receive IVIG or no IVIG in addition to prednisone and cyclofosfamide - the chemotherapy for neuroblastoma. It was noticed that improvement in the assessment of OMAS severity scale was seen in 81% of patients assigned to IVIG compared to no IVIG group (41%).²¹

In this context, Rossor et al proposed a therapeutic algorithm that recommends initiating multimodal treatment within 2 weeks of diagnosis with (1) steroid therapy (prednisolone, ACTH, metiprednisolone pulses, or oral dexamethasone pulses) for one year, (2) IVIG or plasmapheresis, and (3) cyclophosphamide or rituximab. They suggest that this approach improves long-term outcomes and reduces symptom relapses.²²

Even though opsoclonus-myoclonus-ataxia evidenced based treatment is still a challenge to be faced, those findings suggest that the combination of steroid, IVIG and specific chemotherapy for neuroblastoma, where identified, should be the basis of treatment for OMAS.²³

In conclusion, opsoclonus-myoclonus-ataxia syndrome is a rare and little spread neurological condition that has a

close relationship with neuroblastic tumors. We present a case of a one-year-old infant diagnosed with this syndrome, whose first clinical signs were viral prodrome and this way the child was initially conducted as viral encephalitis. This case highlights the importance to discuss this disease in order to guarantee a timely and precise diagnosis and consequently make it possible to give children appropriate treatment and improve long-term outcomes.

ADDITIONAL INFORMATION

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