Case report

Dancing eye syndrome as first symptom of neuroblastoma

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Abstract. *Background:* "Dancing eye syndrome", also called Kinsbourne syndrome or Opsoclonus-Myoclonus-Ataxia Syndrome (OMS) is a rare neurological disorder that in children is frequently associated to occult, low-grade neuroblastoma (NB) (>50% of the cases). OMS may also be triggered by infections and it is often associated to developmental impairment and disability. *Case presentation:* We discuss the case of a 16 months old female with acute onset of OMS associated to occult stage III NB. *Conclusions:* OMS represents a diagnostic challenge for pediatric clinicians. The suspect of OMS imposes the search for an occult NB in order to promptly treat a life-threatening event like tumor and to prevent the neurological consequence linked to OMS. (www.actabiomedica.it)

Key words: Opsoclonus-Myoclonus Syndrome, dancing eye syndrome, neuroblastoma, paraneoplastic neurologic disorder

Introduction

Opsoclonus-Myoclonus-Ataxia Syndrome (OMS), also called "dancing eye syndrome", or Kinsbourne syndrome, is a rare, serious and often chronic neurological disorder that consists of three main symptoms: opsoclonus, characterized by rapid, multi-directional, involuntary eyes saccades, with horizontal, vertical and torsional components; myoclonus, non-epileptic limb jerking that can also involve the head and face and truncal ataxia, which cause gait imbalance. Behavioral changes are often found (1).

OMS is generally a paraneoplastic or parainfectious entity, rarely it is linked to other conditions such toxic, metabolic, or vascular disorders. In many cases, however, no obvious cause is found (i.e. idiopathic opsoclonus). In children, OMS is frequently a manifestation of neuroblastoma (NB) in about 50% of cases and between 2% and 3% of children with NB have OMS (2, 3).

We report the case of a 16 months old infant with classic symptoms of OMS reviewing the literature with the aim of aiding the clinician in the recognition and early management of this disease and the related conditions.

Case presentation

A 16 months-old female with previously normal psychomotor development was admitted in another hospital with uncoordinated limb movements, trunk tremors and strange eye disorder after gastrointestinal infection treated with clobapride, a dopamine antagonist drug with antiemetic and prokinetic properties. Neurologic and ophthalmology evaluations revealed only horizontal nystagmus, without any other abnormalities. Initially an extrapyramidal syndrome secondary to the dopamine antagonist was suspected. Because symptoms did not improve after 1 week she was hospitalized. Due to the presence of neurologic findings the baby underwent a workup for cerebellar dysfunction. Blood exams, including a complete blood count and a basic metabolic panel, were normal, except

for increase in lactic acid dehydrogenase. The patient underwent a lumbar puncture, computed tomography scan and MRI of the head in order to rule out intracranial lesions. Neuroradiological imageries showed no intracranial mass or bleeding and EEG showed non-specific abnormalities of basal rhythm. The cerebrospinal fluid (CSF) physical and chemical properties were normal. Oligoclonal band investigation on CSF and serum revealed a moderate increase consistent with intratecal immunoglobulin synthesis. Infectious investigations including CSF culture and serological test for common viruses were negative. Abdominal ultrasound exam was normal, too. She was empirically treated with ceftriaxone, intravenous immunoglobulin, methylprednisolone and acyclovir. Due to the lack of improvement of neurological symptoms, the patient moved to our hospital. At admission, the child presented with severs opsoclonus and head and severe trunkal ataxia with difficulty to walk without assistance. Based on clinical assessment, the results of the previous exams and the failure to improve with the empirical therapy the baby was diagnosed with OMS. As this condition usually is secondary to a paraneoplastic syndrome, the patient underwent to chest computed tomography scan showing a right paraspinal bulk (Fig. 1). A MIBG-SPET scintigraphy showed accumulation of the radio-drug in an oval formation in the same place in the right posterior-superior mediastinum (Fig. 2). MRI images of mediastinum showed no intra-foramina extension without cord compression, but the lesion was strictly close to large vessels, so it was not possible the surgical eradication (Fig. 3). Histological findings of the lesion

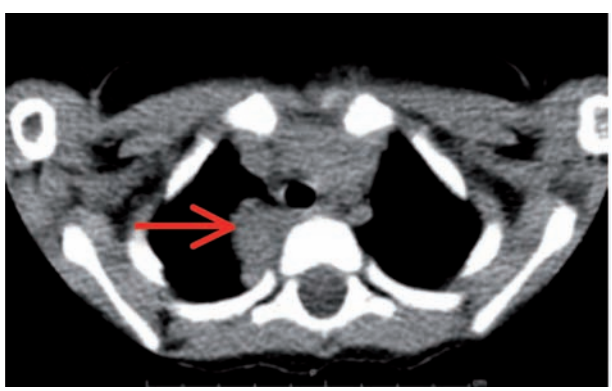

Figure 1. Chest TC: evidence of a 3x2.5x1.7 cm bulk in the right portion of the anterior-superior mediastianum

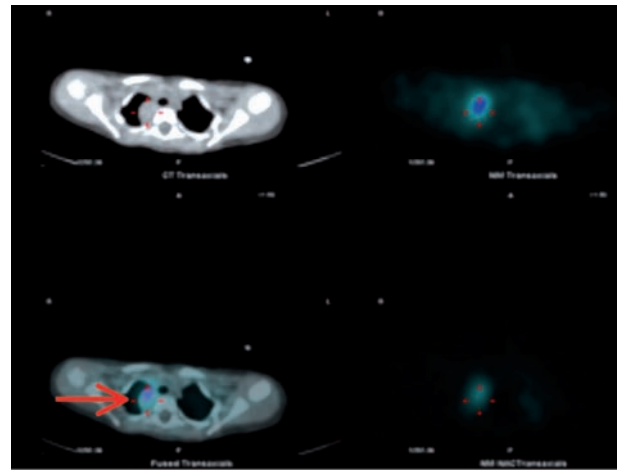

Figure 2. MIBG- SPET scintigraphy: increased uptake of radio-labelled tracer in the right portion of the anterior-superior mediastianum

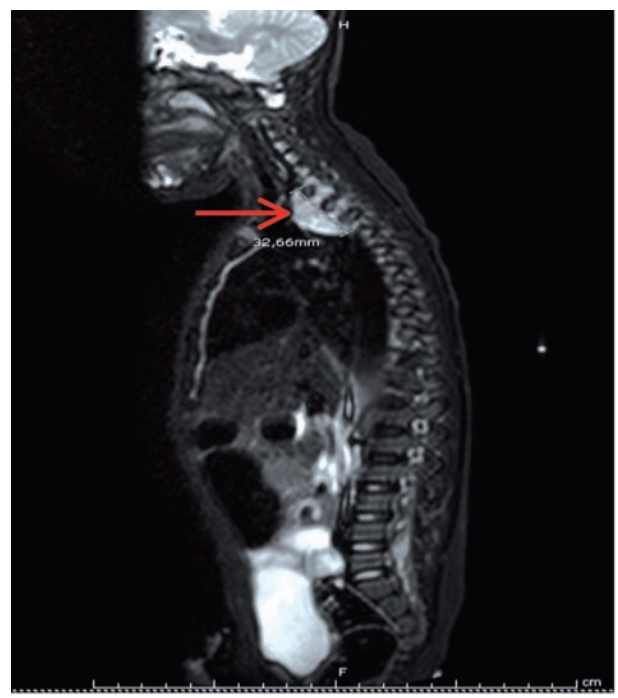

Figure 2. MRI sagittal STIR sequence: expansive extraspinal and extradural mass which extended from D1 to D4-D5 in the right costovertebral recess at the level of the lung apex without vertebral involvement

were consistent with neuroblastoma. Due to the anatomical and histological properties, the NB belongs to stage 3 of the INSS staging system (4). MYCN am-

plification was not found. The baby underwent to chemotherapy regimen as contemplated by AIEOP register for unresectable NB. Three months later, as her OMS symptoms shown only minor improvement with chemotherapy, she started with monthly courses of pulsed high-dose dexamethasone (20 mg/m^2/day for 3 days) for 12 months. After corticosteroids treatment the patient's symptoms resolved. The patient is still followed up regularly, and after three years she has no relapse, neither for OMS nor for NB.

Discussion and conclusion

Opsoclonus myoclonus ataxia syndrome (OMS) of childhood is a rare entity diagnosed primarily between age one and three years with an incidence rate of 0.18 cases per million population per year occurring frequently in patients with NB (5).

Pathophysiology is not clear: autoimmune, humoral and cell mediated immune mechanisms have been implicated (2). In NB-related form, OMS seems to be evocated by an autoimmune response against the cancer and the central nervous tissue, in fact serum antibodies against neurons and cerebellar Purkinje cells have been consistently detected, but their specificity was limited and the target molecules have not been identified yet. This immune response directed against the same molecules expressed by the healthy tissue may cause long term neurological damage, but at the same time may account for the favorable tumor prognosis (6). Anti-Hu antibodies and a specific antineuronal antibody (anti-Ri) were identified in some adult patients affected by OMS associated with small cell lung and breast cancer, respectively (7, 8).

Despite these autoantibodies, the majority of patients with OMS are seronegative for all known antineuronal antibodies; in these cases a cell mediated immune mechanism may be involved. It seems in fact that in cerebrospinal fluid of patients with OMS the count cell is normal, but there is an expansion of CD19+ B-cell and γΔT-cell subsets with a reduced proportion of CD4+ T-cells and reduced CD4/CD8 ratio (2). In the case described we did not look for specific autoantibodies, but we found a moderate increase of oligoclonal band in CSF: this finding could support the autoimmune and humoral hypothesis. At this time none diagnostic bio-marker has been found and a genetic predisposition has been suggested, as many parents of subjects with OMS reported autoimmune disorders (9, 10).

Children with OMS generally present with acute or sub acute onset of ataxia and subsequent sever irritability. The movement disorder is then accompanied by opsoclonus, as in our patient. These symptoms are often associated with neurological impairment, such as irritability, sleeping disturbance and developmental regression. Of note, patients with OMS can also lack any of the classic triad syndrome and exhibit an atypical presentation. Mitchell and Pike developed a grading scale in order to define the OMS severity (Table 1) (11). At diagnosis, the patient of the case described had severe abnormalities, with a score of 13, while a mild to moderate involvement.

The main differential diagnosis is with post-infectious acute cerebellar ataxia. If OMS is suspected, after the exclusion of central nervous system pathology with neuroradiological imaging (MRI) and CSF study, its mandatory the patient undergo to further evaluation in order to rule out a cancer, namely NB, the most common extracranial solid tumor. The search for an occult NB should include imaging of the chest and abdomen (CT scan or MRI), urine catecholamine measurements and metaiodobenzylguanidina scan (12). When negative, the evaluation should be repeated after several months (13).

NB accounts for 7% of malignant tumors in pediatric age, but despite the high frequency, the diagnosis is often delayed because of both its wide presentation heterogeneity and the undervaluation of OMS, seen in 2-3% of children with NB (3, 14). The tumors seen in conjunction with OMS are typically classified as stage I or II without metastases and MYCN amplification (15). Oncological outcome of NB presenting with OMS is generally excellent.

The course of OMS may be remitting and relapsing (16). Treatment and prognosis of OMS is related to the underlying disease and there is no gold standard therapy for OMS. Management of OMS is based on different approaches involving immunosuppressive agents, such as steroids and ACTH, administered in different regimens, as in our patients, some-

Table 1. OMS evaluation criteria (adapted from Matthay et al, 24)

GRADING OF OPSOCLONUS	
0: None	No abnormal eye movements
1: Mild	Abnormal eye movements present, but child can focus on an object, no interference with function
2: Moderate	Abnormal eye movements, limited ability to focus with mild functional impairment
3: Severe	Abnormal eye movements, unable to focus on an object, severe functional impairment
GRADING OF MYOCLONUS/ARM AND HAND FUNCTION	
0: None	No myoclonus
1: Mild	Rarely seen, 1-2 per day
2: Moderate	Several time per day
3: Severe	Sever time per hour, interfering with function
GRADING OF ATAXIA/GAIT	
0: None	Walking normal for age
1: Mild	Mildly wide-based gait for age but able to walk independently
2: Moderate	Walks with support from person or equipment
3: Severe	Unable to walk even with support from person or equipment
GRADING OF ATAXIA/STANCE	
0: None	No ataxia
1: Mild	Mildly unstable standing for age, slightly wide-based
2: Moderate	Unable to stand without support but can sit without support
3: Severe	Unable to sit without support
GRADING OF MOOD/SLEEP DISTURBANCE	
0: None	Normal
1: Mild	Wakes during the night, occasional outbursts
2: Moderate	Poor sleeping and/or irritability or anger/behavioral problems that interfere with daily life
3: Severe	Severe impairment of function by sleep/mood problems

times in combination with intravenous immunoglobulin (17, 18). Relapses of the illness are very common with these regimens (19-21). In the last years the anti CD20 mAb rituximab has been introduced in the treatment of OMS, but the experience with this drug is limited, even if the partial results are encouraging (22-24). Cyclophosphamide and plasmapheresis have been used in order to control neurological symptoms, but despite the efforts 70% of children have a chronic clinical course and develop severe neurological and developmental deficits such as cognitive and motor delays, language deficits and behavioral abnormalities (19, 20, 25-27).

Finally the neurological outcome of pediatric patients with OMS is often compromised: the majority of children experience developmental delays and long-term nervous system dysfunction, which may be devastating (3, 28-30).

OMS is a really rare neurological condition but it is very important to recognize it in order to identify and promptly discover the underlying disease, such NB, a potentially life-threatening conditions ruling out other neurological impairment. Furthermore early recognition of OMS is important because a delay in diagnosis of more than two months is associated with worse neurological, neuropsychological and behavioural outcomes (30)

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