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Original article

Childhood opsoclonus–myoclonus syndrome: A case series from Tunisia

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Abstract

Introduction: Opsoclonus myoclonus syndrome (OMS) is a rare immune-mediated disorder characterized by opsoclonus, myoclonus, ataxia and behavioral changes. The aim of our study was to investigate the epidemiology, clinical features, etiological aspects and outcome of OMS in Tunisian children.

Methods: We conducted a retrospective study over 11 years (2005–2016) including all patients aged under 18 years who were managed for newly diagnosed OMS in a tertiary care research centre for children with neurological symptoms. Epidemiological and clinical data were analyzed.

Results: Fifteen patients were included. The male–female ratio was 7:8. Median age of onset was 4.32 years (range: 14 months–16 years). Time to diagnosis ranged between 2 days and 10 months. Median follow-up period was 3.8 years (range: 2–6 years). Acute ataxia was the preponderant inaugural feature. Mean severity score was 9 (range: 3–14). In "Tumor group" ($n = 7$), the main underlying malignancy was neuroblastoma identified in 5 patient. In "No tumor group" ($n = 8$), parainfectious and idiopathic OMS were identified in 5 and 3 patients, respectively. All patients received immunomodulatory treatment. Complete recovery of OMS symptoms was obtained in 12 children. Comparing the "Tumor group" and the "No tumor group", there were no differences in age of onset, sex ratio, main presenting symptom, median OMS severity score or responsiveness to treatment. However, sleep and behavioral disturbances were more frequent in the "No tumor group" ($p = 0.04$). Neurological sequelae were equally found in both groups.

Conclusion: Annual incidence of OMS in Tunisia could be estimated as 0.6 patients in children per million per year. Diagnosis may be challenging especially when the triad is incomplete. Although behavioral disturbances seem to be more frequent in the "No tumor group", our study suggests that there is no specific features differentiating paraneoplastic OMS from non paraneoplastic OMS. Acute symptoms are responsive to immunomodulatory treatment but long term follow up can reveal neurological (mainly cognitive) sequelae.

Keywords: Opsoclonus myoclonus syndrome; Neuroblastoma; Parainfectious; Paraneoplastic; Hodgkin lymphoma; Rhabdoïd tumor

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1. Introduction

Opsoclonus myoclonus syndrome (OMS) is a rare immune-mediated disorder characterized by opsoclonus, myoclonus, ataxia and behavioral changes [1,2]. It is mainly recognized as a paraneoplastic neurological syndrome [3]. In Tunisia, there is no accurate OMS epidemiological data. In this study, we aimed to investigate the epidemiology, clinical features, etiological aspects and outcome of OMS in Tunisian children.

2. Methods

We conducted a retrospective study over 11 years (2005–2016) including all patients aged under 18 years who were managed for newly diagnosed OMS in a tertiary care research centre for children with neurological disorders (Supplementary data). All patients fulfilled diagnostic criteria of OMS and were followed up for more than 24 months. Severity of neurological symptoms was assessed by the OMS severity scale (Supplementary data). Two groups were considered: the first one included patients with identified tumor or "Tumor group" and the second included patients with unidentified tumor or "No tumor group". Variables were compared among both groups using Student *t*-test, *p* values lower than 0.05 were considered statistically significant.

3. Results

Fifteen OMS patients were identified (Table 1). The male–female ratio was 7:8. Median age of onset was 4.32 years (range: 14 months–16 years). Median time to diagnosis was 4.2 months (range: 2 days–10 months). Ataxia was noticed in all patients and it was the preponderant inaugural symptom (12 cases) (Table 1). The opsoclonus was observed in 13 patients and was whether concomitant to ataxia or with delayed onset (range: 15 days–6 months). Myoclonus was present in 11 patients and was often concomitant to ataxia. Behavioral changes (irritability, impulsivity, agitation, apathy) and/or sleep disturbances were reported in 7 patients. Mean severity OMS score evaluated in 12 patients was 9 (range: 3–14).

Routine biological tests were normal in all patients. Cerebrospinal fluid (CSF) examination was performed in 10 patients and showed high protein level in 2 patients (8 and 14). All patients had brain magnetic resonance imaging (MRI), which was normal in 13 cases and showed unspecific periventricular white matter changes on T2 and Fluid-Attenuated Inversion Recovery (FLAIR) weighted images in 2 patients (8 and 14). A screening for toxic drug intake was performed in all patients with acute ataxia and was negative. Other biological investigations (α-foeto-protein, vitamin E, ammonia, lactate (serum and CSF)…) were performed in patients with isolated ataxia at onset, and were in normal range, which excluded other pediatric neurological disorders manifesting with cerebellar ataxia.

Patients were classified according to the underlying etiology in two groups (Table 2): paraneoplastic origin or the "Tumor group" ($n = 7$) and non paraneoplastic origin or the "No tumor group" ($n = 8$) including the parainfectious ($n = 5$) and the idiopathic ($n = 3$) subgroups. Serum and CSF analysis for infectious agents (Herpes Simplex virus (HSV), Epstein-Barr virus (EBV), Varicella Zoster virus (VZV), Cytomagalovirus CMV, rubella virus, mumps morbillivirus, Human Immunodeficiency virus (HIV), mycoplasma pneumoniae and Borrelia burgdorferi) performed in all patients, were positive in patients 10, 11 and 12 (EBV, borrelia burgdorferi and rubella virus respectively). Neuron specific enolase (NSE) level was determined in 11 patients and was increased in all of them during the acute phase. However, repetitive bioassay of NSE (3 months interval) was normal in the "No tumor group", whereas persistent high levels were noticed in the "Tumor group". Vanillylmandelic acid (VMA) level, performed in 6 patients, was high in only one case with neuroblastoma. Antineuronal antibodies (anti-Amphiphysin, anti-Hu, anti-Yo, anti-Ri, anti-CV2 and anti-Ma2) were tested in 9 patients and were negative. Extensive screening for underlying tumor performed in all patients (including ultrasonography, thoraco-abdomino-pelvic CT scan, whole body MRI and iodin e-123-meta-iodobenzylguanidine (MIBG) scintigraphy) provided evidence of tumor in only 7 patients.

The underlying malignancies in the "Tumor group" were neuroblastoma in 5 cases, Hodgkin lymphoma and rhabdoïd skin tumor in one case respectively (Table 1). OMS preceded the tumor diagnosis in 6 patients. However, neurological symptoms appeared one month later after tumor removal in patient 4. In the "No tumor group, parainfectious" OMS was diagnosed in 5 patients and idiopathic OMS was considered in 3 children (Table 1).

All patients received methylprednisolone pulse (30 mg/kg/day × 5 days) followed by oral steroids (1–2 mg/kg/day). Intravenous immunoglobulins (IVIG) (0.4 g/kg/day × 5 days) were administrated in only one patient (Table 1). Time to treatment was often less than two weeks and oncological treatment was based on surgery in 2 cases, chemotherapy in one case and both surgery and chemotherapy in 4 cases.

Median follow-up period was: 3.8 years (range: 2–6 years). Complete recovery of OMS symptoms was obtained in 12 children. Motor sequelae (mild cerebellar ataxia with OMS score ≤ 2) were present in 3 patients and neuropsychological dysfunction (cognitive decline, speech delay and learning disabilities) were noticed in 5 patients.