Opsoclonus-myoclonus syndrome: Experience in a tertiary hospital in the last 12 years☆

Síndrome *opsoclonus mioclonus*. Experiencia en los últimos 12 años en un hospital terciario

To the Editor

Opsoclonus myoclonus syndrome (OMS) is a neuroimmune syndrome defined by the presence of at least 3 out of 4 clinical criteria: opsoclonus or ocular flutter; neuroblastoma; myoclonus and/or ataxia; behavioural change and/or sleep disturbances frequently associated with marked irritability.[1] Its incidence is estimated at 0.27 to 0.40 cases per million children.[2] In up to 50% of cases, it is associated with neural crest cell tumours. It is suspected that the actual frequency of this association may be higher, but that some may not ever be detected due to having been destroyed by a possible immune response.[3] In the absence of a tumour, an infectious aetiology has been proposed, although it would be difficult to establish a causal relationship, and therefore it may be preferable to refer to a cryptogenic or idiopathic aetiology. In either case, it appears that the symptoms may be immune-mediated, with the immune system attacking the nervous system at the brainstem or cerebellum, but also possibly at a supratentorial level.[4]

Although development is normal in some patients after OMS, there is also a significant proportion that exhibit cognitive or neurodevelopmental impairment (affecting attention, memory, visual-motor skills...) during the follow-up, usually with normal or nearly normal motor outcomes.[2,5] Factors such as a younger age at diagnosis, delayed initiation of immunosuppression, severe presentation at onset or recurrence are considered potential predictors of a poor outcome. In recent years, the approach to the management of OMS has changed, with current approaches favouring early intensification of immunosuppression, initiating treatment with a combination of 2 drugs (usually steroids and immunoglobulin), with early addition of a second-line drug if the response is not satisfactory. Some authors even propose triple therapy as the initial approach.[6] These approaches aim at improving control of the immune component of the disease in order to resolve the acute neurologic manifestations and, above all, to minimise cognitive sequelae.

We describe a series of cases of OMS diagnosed between 2006 and 2018 in patients evaluated and followed up in a neuroimmune disease clinic. We analysed clinical and epidemiological characteristics of the cases, the treatment used and the medium- to long-term outcomes (Table 1).

In our cohort, we found a slight predominance of the female sex in patients with OMS (62.5%) and a mean age of 18.8 months, similar to the findings in previous series.[3]

Ataxia was the most frequent symptom at onset, followed by opsoclonus. Onset with isolated ataxia[3] poses a challenge in the differential diagnosis with acute post-infectious cerebellar ataxia, a disease with a higher incidence that tends to manifest at a slightly older age and preceded more frequently by prodromal manifestations compared to OMS. The presence of other cardinal motor symptoms clearly facilitates the diagnosis of OMS, while their absence or delay complicates it. In our series, one of the patients (patient 4) did not develop myoclonus or opsoclonus, and it was the behavioural changes that allowed the diagnosis of OMS and detection of a neuroblastoma. Opsoclonus myoclonus syndrome must be contemplated as a potential diagnosis in case of persistent acute ataxia associated with behavioural changes, even in the absence of other cardinal motor symptoms.

The frequency of paraneoplastic cases (50%) was similar to the frequencies reported in previously published case series worldwide.[3] The tumour was detected in the initial screening in all patients, although in 2 the metaiodobenzylguanidine scintigraphy scan and the urine catecholamine test were normal, as well as the abdominal ultrasound scan in one of them, and the tumour was only detected by magnetic resonance imaging. Since the tumours associated with OMS are usually low-grade, tests that depend on metabolic activity may not be sensitive enough for diagnosis, and thus should be accompanied by standardised imaging tests. Also, due to their small size, these tumours may not be detectable in plain radiographs or ultrasound scans.[3,4]

In our series, some of the patients with a medium- to long-term follow-up exhibited a degree of neurocognitive impairment, although in most it was less severe than described historically. In the group of patients that remained free of OMS symptoms, the proportion that exhibited cognitive impairment at 2 years of follow-up was similar in those that had onset before age 18 months (2/3) and those that had onset later (2/3). Patients that developed some form of cognitive sequelae (patients 4–6) had onset at the same or a slightly older age compared to patients that did not exhibit cognitive changes (patients 1–3).

Of the 3 patients with a normal cognitive assessment 2 years from onset, 2 (patients 1 and 2) only required bitherapy for complete control of symptoms, although they were the only patients with paraneoplastic cases that received chemotherapy. This could support the hypothesis proposed by some authors that the better outcomes observed in paraneoplastic cases could be due, at least in part, to a beneficial effect of chemotherapy in the control of the autoimmune-inflammatory basis of the disease. The other patient free of cognitive impairment (patient 3) was the only patient that did not receive bitherapy from the outset. The cardinal symptoms in this patient proved difficult to control, requiring prolonged and steroid-sparing immunotherapy, although this was also the patient in who triple therapy was initiated earliest, with addition of rituximab 5 months after onset of OMS, at age 19 months. The absence of cognitive sequelae in this patient is worth highlighting, given the difficult control of OMS symptoms and the relatively early onset. In the other patients that required triple therapy, the third agent was added at ages 53, 32 and 23 months (patients 4, 5 and 7) between 10 and 26 months from initiation of treatment. Patient 7 was the patient with the earliest onset and greatest diagnostic delay, and he continues to have symptoms and has the greatest degree of psychomotor and cognitive

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Table 1 Clinical and epidemiological characteristics and approach to treatment.

Case number Current age	Sex	Age at onset/ duration of follow-up	Prodrome	Time to DX	Onset SX	SX during follow-up	Aetiology (+/− TX)	Initial immunos-uppression (total doses)	Time to combination TX	2nd line drug (time from DX)	Mitchell/ Pranzatelli scale: 0/6/12/24 months	Time to SX resolution /current symptoms	Initial neurode-velopmental evaluation	Last neurode-velopmental evaluation (chronologi-cal age, time from onset)
Pt 1	M	16 m/2.8 y	Fever 48 h	1.5 m	Ataxia	Opsoc, myoc,	NB	IVIG cycles (15) + DXM pulses (4)	0	No	-/2/1/0	12 m	Normal	Normal. DQ 93 (CA 2.5 y; TO 1.2 y)
4 y 2 m						BX D, tremors	(surgery and CTX)				29/1.5/2/0			
Pt 2	F	19 m/3.2 y	No	0.5 m	Ataxia	Opsoc, myoc,	GNB	IVIG cycles (21) + DXM pulses (10)	0	No	-/1/0/0	4 m	Mild global developm-ental delay (CD 73)	Normal. IQ 94, VCI 96, VSPI 82, FRI 100, WMI 87, PSI 86 (CA 4 y; TO 2.6 y)
4 y 10 m						BX D, sleep D, speech D	(CTX)				18/1/0/0			
Pt 3	F	14 m/2.7 y	No	0.3 m	Opsoc	Ataxia, myoc,	Cryptogenic	Cycles DXM pulses (26)	4 m	Rituximab (4 m). 2nd dose (12 m)	12/9/4/0	18 m	Mild global developm-ental delay (CD 86)	Normal. IQ 106, VCI 112, VSPI 103, WMI 91 (CA 3 y; TO 2.1 y)
3 y 11 m						BX D, sleep D, speech D, tremors			(+ IVIg) (27)		29/28/4/0			
Pt 4	M	27 m/7.8 y	Laryngitis	1 m	Ataxia	BX D,	NB	IVIG cycles (12)	0	Rituximab (26 m)	-/-/-/5	55 m	Non-standard evaluation	Non-standard evaluation. ADHD DX, good response to MPH (current)
10 y 1 m						sleep D, speech D, tremors	(Surgery)	Oral PDN			12/-/-/12			
Pt 5	F	22 m/7.6 y	No	0.2 m	Ataxia	Opsoc, myoc,	Cryptogenic	IVIG cycles (13) + ACTH→ oral PDN →DXM pulses (10)	0	Cyclopho-sphamide (10 m)	-/-/4/1	30 m	IQ 98, attention and motor skill deficits	CIT 116, IQ 125, FRI 116, WMI 114, PSI 88. Executive functioning deficits, with attention deficit, impulsivity, fidgeting. Adequate academic performance (CA 7.6 y; TO 6 y)
9 y 4 m						sleep D, speech D, tremors					-/-/8/1			

Table 1 (*Continued*)

Case number Current age	Sex	Age at onset/ duration of follow-up	Prodrome	Time to DX	Onset SX	SX during follow-up	Aetiology (+/− TX)	Initial immunos-uppression (total doses)	Time to combination TX	2nd line drug (time from DX)	Mitchell/ Pranzatelli scale: 0/6/12/24 months	Time to SX resolution /current symptoms	Initial neurode-velopmental evaluation	Last neurode-velopmental evaluation (chronologi-cal age, time from onset)
Pt 6	F	17 m/12.5 y	No	2 m	Opsoc	Myoc, ataxia,	NB 8 m before OMS	IVIG cycles (12)	0	No	-/-/-/-	17 m	DQ 90. High emotional reactivity, BX D, impaired attention	IQ 86, VCI 92, VSPI 84, FRI 94, WMI 97, PSI 95. ADHD, mainly impulsivity with progression to oppositional/ defiant behaviour. School failure (CA 13 y; TO 11.5 y)
13 y 9 m						BX D, sleep D, tremors	(Surgery)	Oral DXM			14/14/13/4			
Pt 7	M	6 m/2.3 y	No	8 m	Opsoc	Ataxia, myoc,	Cryptogenic	IVIG cycles (7) + DXM pulses (6)	0	Rituximab (8 m)	12/12/10/-	Ataxia, limited language	Non-standard evaluation. Global devel-opmental delay	Pronounced global devel-opmental delay (failure to achieve unsupported standing, familiar two-syllable words) DQ 56 (current)
2 y 10 m						BX D, sleep D, speech D (preverbal), tremors					33/24/27/25			
Pt 8	F	30 m/4 m	Rhinovirus + RTI	1 m	Ataxia	Opsoc,	Cryptogenic (parainfec-tious)	IVIG cycles (5) + DXM pulses (5)	0	Rituximab (2.5 m)	6	Ataxia, resolving	Normal	No follow-up evaluation (4 m from onset)
2 y 10 m						BX D, speech D, tremors					13			

ACTH, corticotropin; ADHD, attention-deficit hyperactivity disorder; BX D, behavioural disorder; CA, chronological age; CTX, chemotherapy; DG, global development quotient, based on the Batelle Developmental Inventory; DX, diagnosis; DXM, dexamethasone; F, female; FRI, fluid reasoning index; GNB, ganglioneuroblastoma; IQ, total intellectual quotient score obtained with the Wechsler Preschool & Primary Scale of Intelligence (WPPSI) or the Wechsler Intelligence Scale for Children (WISC) depending on age; IVIG, intravenous immunoglobulin; M, male; myoc: myoclonus; NB, neuroblastoma; OMS, opsoclonus-myoclonus syndrome; opsoc, opsoclonus; PDN, prednisone; PSI, processing speed index; Pt, patient; RTI, respiratory tract infection; Sleep D, sleep disorder; Speech D, speech disorder; SX, symptom; TO, time from onset; TX, treatment; VCI, verbal comprehension index; VSPI, visual-spatial processing index; WMI, working memory index.
-: scale not administered at given timepoint.

impairment compared to the same timepoint in the follow-up in all other patients in the series. The other 2 patients developed attention-deficit hyperactivity disorder (ADHD), but this did not have an impact on academic performance in one, and the other responded well to stimulant medication. On the other hand, the other patient that exhibited the most severe cognitive and behavioural impairment (patient 6) only received bitherapy, with maintenance steroid therapy given orally.

Opsoclonus-myoclonus syndrome is an immune-mediated disease, in some cases associated with an underlying tumour, in which early treatment and appropriate intensification may have an impact on medium- to long-term outcomes (especially in cognitive development). Due to all of the above, despite its low incidence, this syndrome should be contemplated in patients with acute onset of any of its typical features, especially ataxia. If we analyse the evolution of patients over time and the treatment regimens used, it appears possible that an improved understanding of the disease and the importance of early treatment and intensification contributed to changes in our management of OMS. However, there are considerable limitations to our study, given its retrospective design and small sample. As a consequence, it was not possible for us to establish the association between changes in treatment and neurocognitive outcomes, which would require a prospective study with a pre-established treatment protocol. However, we believe that our findings are relevant, as they provide information on clinical experiences that may contribute to a better understanding of this disease.

References

1. Matthay KK, Blaes F, Hero B, Plantaz D, De Alarcon P, Mitchell WG, et al. Opsoclonus myoclonus syndrome in NB a report from a workshop on the dancing eyes syndrome at the advances in NB meeting in Genoa, Italy, 2004. Cancer Lett. 2005;228:275–82.
2. Hasegawa S, Matsutake T, Kajimoto M, Inoue H, Momonaka H, Oka M, et al. A nationwide survey of opsoclonus-myoclonus syndrome in Japanese children. Brain Dev [Internet]. 2015;37:656–60.
3. Pranzatelli MR, Tate ED, McGee NR. Demographic, clinical, and inmunologic features of 389 children with Opsoclonus-Myoclonus Syndrome: a cross-sectional study. Front Neurol. 2017;8:468.
4. Pranzatelli MR, Tate ED. Opsoclonus myoclonus syndrome. In: Swaiman K, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, et al., editors. Swaiman's Pediatric Neurology: Principles and Practice (Chap 120). London, UK: Elsevier; 2017. p. 938–44.
5. Mitchell WG, Wooten AA, O'Neil SH, Rodriguez JG, Cruz RE, Wittern R. Effect of increased immunosuppression on developmental outcome of Opsoclonus Myoclonus Syndrome (OMS). J Child Neurol. 2015;30:976–82.
6. Pranzatelli MR, Tate ED, McGee NR, MacArthur CA. Evaluation of responsiveness to reduced-dose rituximab in corticotropin/intravenous immunoglobulin/rituximab combination immunotherapy for Opsoclonus-Myoclonus Syndrome. Pediatr Neurol. 2018;85:71–5.

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