Brain (2001), **124,** 437–443

Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus–myoclonus

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Summary

We analysed a series of 24 adult patients with idiopathic (10 cases) and paraneoplastic (14 cases) opsoclonus–myoclonus syndrome (OMS) to ascertain possible differences in clinical course and response to immunotherapies between both groups. Associated tumours were small-cell lung cancer (SCLC) (nine patients), non-SCLC (one patient), breast carcinoma (two patients), gastric adenocarcinoma (one patient) and kidney carcinoma (one patient). Patients with paraneoplastic OMS were older [median age: 66 years versus 40 years ($P = 0.006$) of those with idiopathic OMS] and had a higher frequency of encephalopathy (64% versus 10%; $P = 0.02$). Serum from 10/10 idiopathic and 12/14 paraneoplastic OMS patients showed no specific immunoreactivity on rat or human brainstem or cerebellum, lacked specific antineuronal antibodies (Hu, Yo, Ri, Tr, glutamic acid decarboxylase, amphiphysin or CV2) and did not contain antibodies to voltage-gated calcium channels. The two paraneoplastic exceptions were a patient with SCLC, whose serum contained both anti-Hu and anti-amphiphysin antibodies and a patient with breast cancer who had serum anti-Ri antibodies. The clinical course of idiopathic OMS was monophasic except in two elderly women who had relapses of the opsoclonus and mild residual ataxia. Most idiopathic OMS patients made a good recovery, but residual gait ataxia tended to persist in older patients. Immunotherapy (mainly intravenous immunoglobulins or corticosteroids) seemed to accelerate recovery. Paraneoplastic OMS had a more severe clinical course, despite treatment with intravenous immunoglobulins or costicosteroids, and was the cause of death in five patients whose tumours were not treated. By contrast the eight patients whose tumours were treated showed a complete or partial neurological recovery. We conclude that idiopathic OMS occurs in younger patients, the clinical evolution is more benign and the effect of immunotherapy appears more effective than in paraneoplastic OMS. In patients aged 50 years and older with OMS who develop encephalopathy, early diagnosis and treatment of a probable underlying tumour, usually SCLC, is indicated to increase the chances of neurological recovery. At present, there are no immunological markers to identify the adult patients with paraneoplastic OMS.

Keywords: paraneoplastic; opsoclonus–myoclonus; immunotherapy; autoantibodies.

Abbreviations: IVIG = intravenous immunoglobulins; LEMS = Lambert–Eaton myasthenic syndrome; OMS = opsoclonus–myoclonus syndrome; SCLC = small-cell lung carcinoma; VGCC = voltage-gated calcium channels

Introduction

The opsoclonus–myoclonus syndrome (OMS) is characterized by subacute onset of opsoclonus, a disorder of saccadic eye movements causing involuntary, chaotic saccades that occur in all directions (Leigh and Zee, 1999). Opsoclonus is usually associated with arrhythmic-action myoclonus that predominantly involves the trunk, limbs and head (Caviness *et al.*, 1995). Some patients also have cerebellar dysfunction with dysarthria and truncal ataxia and a few become confused

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or even comatose. OMS is associated with multiple aetiologies and in two clinical settings: paraneoplastic and idiopathic, the pathophysiology may be autoimmune (Pranzatelli, 1992).

In a given patient with OMS, once the known causes are ruled out in the initial evaluation, the diagnosis of paraneoplastic or idiopathic OMS must await the clinical evolution and the discovery of a possible underlying neoplasm: neuroblastoma in children and small-cell lung carcinoma (SCLC), or breast cancer in adults (Dropcho and Payne, 1986; Anderson *et al.*, 1988; Luque *et al.*, 1991). Previous studies have not found useful clinical or laboratory features to identify the OMS as paraneoplastic or idiopathic. An exception is the presence of anti-Ri antibodies in patients with OMS and breast cancer (Luque *et al.*, 1991). Similarly, the response to different immunotherapies is unclear in paraneoplastic and idiopathic OMS because the rarity of this disorder hinders controlled clinical studies and the possibility of spontaneous remissions makes interpretation difficult in isolated cases. In patients with Lambert–Eaton myasthenic syndrome (LEMS), immunotherapy seems more effective in those patients without cancer, whereas in those with SCLC treatment of the tumour is important to achieve control of the myasthenic syndrome (Newsom-Davis and Murray, 1984; Chalk *et al.*, 1990). Whether this difference holds true for the OMS is presently unknown.

The present study retrospectively analyses a series of adult patients with OMS to ascertain possible differences in the clinical and immunological features and response to immunotherapy between the idiopathic and paraneoplastic cases.

Methods

Patients

Since 1985, 10 patients with idiopathic or paraneoplastic OMS have been diagnosed by two of the authors (J.J.V. and F.G). As a consequence of a special common interest in OMS a collaborative Spanish survey was carried out as follows. We identified patients with OMS whose serum/CSF samples were sent to the laboratory of the Service of Neurology, Hospital Clínic (Barcelona) for detection of anti-neuronal antibodies. Patients fulfilling the following criteria were included in our study: (i) age more than 18-years-old; (ii) presence of an ocular movement disorder compatible with opsoclonus, with or without myoclonus, ataxia or encephalopathy; (iii) absence of evidence of structural or infectious disease of the central nervous system, and of toxic or metabolic disorders known to be related to opsoclonus.

We asked the referring neurologists to retrieve from the clinical records information about the neurological symptoms, treatments given for the OMS and the clinical course according with a standardized questionnaire that was sent to all the participants in the study. Two different groups were defined. (i) Paraneoplastic OMS: patients with a tumour discovered at the time or shortly after the onset of the OMS. (ii) Idiopathic OMS: patients without known cancer after $>$ 2 years of follow-up and no other definitive cause for the OMS. Two patients who died shortly after the onset of OMS without autopsy to rule out an occult neoplasm were excluded. The results were discussed in a meeting held with the referring neurologists before the final analysis.

Table 1 *Demographic and clinical characteristics of patients with idiopathic or paraneoplastic OMS*

	Idiopathic $n = 10$ (%)	Paraneoplastic $n = 14$ (%)
Median age (range) (years)*	40 (24–80)	66 (53–75)
Male : female	5 : 5	12 : 2
Opsoclonus	10 (100)	14 (100)
Myoclonus	7 (70)	10 (71)
Truncal ataxia	10 (100)	14 (100)
Limb ataxia	4 (40)	5 (36)
Dysarthria	4 (40)	8 (57)
Encephalopathy**	1 (10)	9 (64)

*$P = 0.02$ (Student's t-test); **$P = 0.006$ (Fisher's exact test).

Immunological methods

Serum and CSF, when available, were evaluated for the presence of anti-neuronal antibodies (Hu, Yo, Ri, Tr, CV2, amphiphysin and glutamic acid decarboxylase) or new neuronal-specific antibodies by immunohistochemistry on frozen sections of rat and human brainstem and cerebellum and immunoblot of rat brain homogenate according to standardized techniques previously reported in detail (Graus *et al.*, 1997; Saiz *et al.*, 1997). Antibodies to voltage-gated P/Q-calcium channels (VGCC) were analysed by a commercial [^{125}I][omegabar]-CmTx–VGCC assay following the manufacture's guidelines (DLD Diagnostika, Hamburg, Germany). Ten patients with LEMS and 20 with degenerative neurological syndromes were used as positive and negative controls of the assay.

Results

Twenty-four patients fulfilled the required criteria. The clinical features of idiopathic and paraneoplastic OMS are summarized in Tables 1–3. Patients with idiopathic OMS were younger than those of paraneoplastic origin. Median age of the idiopathic group was 40 years and that of the paraneoplastic 66 years ($P = 0.006$) (Table 1). Encephalopathy was more frequent in the paraneoplastic group ($P = 0.02$). Only one patient (Case 6) in the idiopathic group showed slight disorientation and inattention. In contrast, nine patients with paraneoplastic OMS presented a severe encephalopathy that led to death in five of them (Cases 11, 18, 19, 20 and 23).

No previous febrile syndrome was recorded in any case. CSF examination was normal or disclosed a mild pleocytosis (median 9 lymphocytes; range 0–65) with no differences

Table 2 *Clinical course and response to immunotherapy in patients with idiopathic OMS*

Patient	Age (year)/sex	Course	Immunotherapy	Time to improvement	Final status (follow-up)
1	24/F	Monophasic	Corticosteroids	< 3 months	Asymptomatic (5 years)
2	31/F	Monophasic	IVIG	< 3 months	Asymptomatic (2 years)
3	33/F	Monophasic	No	> 3 months	Asymptomatic (4.5 years)
4	34/M	Monophasic	IVIG	< 3 months	Asymptomatic (2 years)
5	36/M	Monophasic	No	< 3 months	Asymptomatic (5 years)
6	45/M	Monophasic	Corticosteroids/IVIG	> 3 months	Mild truncal ataxia (2.5 years)
7	50/M	Monophasic	Corticosteroids	> 3 months	Asymptomatic (4 years)
8	53/M	Monophasic	Azathioprine	> 3 months	Mild truncal ataxia(10 years)
9	76/F	Relapsing	IVIG at relapse	Remission (see text)	Mild truncal ataxia (4 years)
10	80/F	Relapsing	IVIG at relapse/azathioprine	Remission (see text)	Mild truncal ataxia (6 years)

M = male; F = female; IVIG = intravenous immunoglobulins.

between idiopathic or paraneoplastic OMS. All patients had a normal brain CT or MRI scan except Patient 1 whose MRI showed an area of T_2-increased signal in the left thalamus that disappeared in a control MR 2 weeks after steroid treatment.

Serum from idiopathic and OMS patients lacked a consistent immunoreactivity against human or rat brainstem and cerebellum. All patients with idiopathic OMS lacked antineuronal and anti-VGCC antibodies. Two patients with paraneoplastic OMS had antineuronal antibodies: one patient with SCLC (Case 11) had both anti-amphiphysin antibodies and low titres of anti-Hu antibodies. These were in the range found in 16% of SCLC patients without paraneoplastic neurological disorders (Dalmau *et al*., 1990). Anti-Ri antibodies were found in one of the two patients with OMS and breast cancer (Case 21). No patient with paraneoplastic OMS harboured anti-VGCC antibodies.

Clinical course and response to immunotherapy in patients with idiopathic OMS

Eight patients (Cases 1–8) had a monophasic course of the OMS (Table 2). The OMS resolved completely in the five patients younger than 40 years of age. Two of these five patients did not receive any immunotherapy and in one the OMS took >3 months to disappear. By contrast, the other three patients were treated with steroids (one) or intravenous immunoglobulins (IVIG) and all made a recovery in <3 months. The three patients older than 40 years of age made a slow improvement receiving treatment with azathioprine, steroids or IVIG plus steroids. These three patients also received, respectively, clonazepam, chlormethiazole, and a combination of valproic acid, clonazepam and piracetam.

The other two patients with idiopathic OMS followed a relapsing clinical course (Cases 9 and 10). They were two women 76 and 80 years of age who presented recurrent episodes of opsoclonus that dramatically improved after IVIG treatment. Both patients had a mild gait ataxia between the relapses. The clinical evolution of these two patients is exemplified by the report of Case 10.

An 80-year-old woman was evaluated in February 1994 because of gait imbalance that had evolved over the previous months. On examination there was an ataxic gait. The rest of the neurological examination was normal. There was no previous family history of neurological disorder. Routine blood and CSF analysis, chest X-ray, thyroid hormones, antinuclear antibodies and brain MR were unremarkable. One year later, the patient complained of oscillopsia and increased gait instability. The neurological examination showed opsoclonus and severe gait ataxia without myoclonus. A new cerebral MR, CSF analysis and an extensive study searching for an occult neoplasm were negative. She was started on azathioprine with a slow improvement over the ensuing months. In November 1996, there was a relapse of opsoclonus and worsening of ataxia. She received IVIG (0.4 g/kg over 5 days) with dramatic improvement, as on the third day of treatment opsoclonus had almost disappeared. In July 1997, there was a new relapse of opsoclonus, which again improved after IVIG. To date this patient has stabilized with a mild gait imbalance and no ocular abnormalities.

Clinical course and response to immunotherapy in patients with paraneoplastic OMS

The onset of OMS preceded the tumour diagnosis in all but one patient with SCLC (Case 18). Four of the 10 patients with lung cancer did not receive antineoplastic treatment and the OMS progressed to severe encephalopathy and death in all the patients in spite of treatment with plasmapheresis, IVIG or steroids. The tumour was not treated because the oncologist felt the patient was too ill to receive chemotherapy (three patients), or the tumour was found at the autopsy (one). By contrast, the other six patients received antineoplastic treatment. Four of these patients achieved a complete and two a partial response of the SCLC and the OMS improved in all, although five patients had a mild residual gait ataxia. Three of these six patients did not receive any immunotherapy besides the treatment of the cancer. The other three received

Table 3 *Clinical course and response to immunotherapy in patients with paraneoplastic OMS*

Patient	Age/sex (years)	Time to tumour diagnosis	Cancer	Response of opsoclonus–myoclonus to therapies				Final status (follow-up)
				Immunotherapy		Antineoplastic		
				Type	Response	Treatment	Response	
11	69/M	1 month	SCLC	Steroids, IVIG	No response	No	NA	Death due to encephalopathy (1 month)
12	65/M	1 month	SCLC	No	NA	Yes	Complete	Alive and asymptomatic (17 months)
13	54/M	1 month	SCLC	No	NA	Yes	Partial	Residual mild truncal ataxia. Dead from SCLC (22 months)
14	61/M	1 month	SCLC	Steroids	No response	Yes	Partial	Residual mild truncal ataxia. Dead from SCLC (11 months)
15	60/M	6 months	SCLC	No	NA	Yes	Partial	Residual mild truncal ataxia. Dead from SCLC (18 months)
16	62/M	5 months	SCLC	Steroids	Partial	Yes	Partial	Alive with mild truncal ataxia (39 months)
17	53/M	1 month	SCLC	Steroids, IVIG	No response	Yes	Partial	Alive with mild truncal ataxia (6 months)
18	60/M	–0.5 months	SCLC	Plasmapheresis	No response	No	NA	Death due to encephalopathy (3 months)
19	75/M	1 month	SCLC	IVIG	No response	No	NA	Death due to encephalopathy (3 months)
20	67/M	3 months	NSCLC	Steroids	No response	No	NA	Death due to encephalopathy (6 months)
21	65/F	1 year	Breast	No	NA	Yes	Complete	Alive and asymptomatic (14 years)
22	61/F	1 month	Breast	Steroids, IVIG*	Partial	Yes	Partial	Alive with mild truncal ataxia (3 years)
23	59/M	1 month	Gastric	Steroids	No response	No	NA	Death due to encephalopathy (6 months)
24	64/M	6 months	Kidney	Steroids	Complete	No†	NA	Alive and asymptomatic (5 years)

NA = not applicable; M = male; F = female; SCLC = small-cell lung cancer; NSCLC = non-small-cell lung cancer; IVIG = intravenous immunoglobulins. *Given at the same time as tumour treatment; †tumour treated at remission of the OMS.

steroids, one also IVIG, before starting chemotherapy and only one made a partial improvement of the OMS.

In the two cases with breast cancer, there was a slow and complete remission of the OMS after treatment of the neoplasm in one patient. The second patient (Case 22) received IVIG and steroids and at the same time had surgery and adjuvant chemotherapy for the breast cancer. The OMS improved slowly over the ensuing 12 months leaving the patient with a mild gait ataxia. Patient 23 presented with OMS and signs of severe encephalopathy. The neurological condition worsened despite treatment with IVIG and the post-mortem study disclosed a local infiltrating gastric adenocarcinoma. Lastly, Patient 24, previously described (Koukoulis *et al*., 1998), developed an OMS which completely recovered in a few weeks after steroid treatment. Six months later, an abdominal CT showed a renal adenocarcinoma which was successfully removed and the patient remains asymptomatic 5 years later.

Discussion

The current retrospective study shows some important differences in the clinical symptoms and outcome to treatment between paraneoplastic and idiopathic adult OMS. Idiopathic OMS occurs in younger patients, the clinical evolution is more benign and the effect of immunotherapy seems more effective than in paraneoplastic OMS.

Patients with idiopathic OMS were younger than those with paraneoplastic OMS and no patient with paraneoplastic OMS was under 50 years old. However, in older patients there were no clear clinical features to predict the cause of OMS. We found an age-dependent prognosis in the long-term clinical course of idiopathic OMS. In general, older patients had a slower improvement and were predisposed to remain with residual permanent neurological deficits, mainly gait ataxia. Evolution of the idiopathic OMS to coma and death is exceptional and usually reported in patients older than 60 years (Digre, 1986). Although idiopathic OMS in adults tends to follow a monophasic course, we have observed two elderly women with a chronic relapsing evolution highly responsive to IVIG. This relapsing–remitting profile had been observed in paraneoplastic but not in idiopathic OMS (Anderson *et al*., 1988; Digre 1986; Honnorat *et al.*, 1997). Therefore, the present observation indicates that this clinical course does not necessarily imply a paraneoplastic origin of the OMS.

Idiopathic OM has been empirically treated with a number of immunotherapies with varying results (Pranzatelli, 1992; Pless and Ronthal, 1996). Some authors have suggested that no treatment is necessary in idiopathic OMS since symptoms tend to abate in a few weeks without therapy (Digre, 1986). However, the rarity of idiopathic OMS will prevent the design of randomized studies that demonstrate the beneficial effect of IVIG as in the Guillain–Barré syndrome. Our retrospective study and previous case reports (Pranzatelli, 1992; Pless and Ronthal, 1996) suggests patients with idiopathic OMS treated with different immunotherapies may have a faster recovery and this treatment should be recommended particularly in those cases with a severe neurological dysfunction.

Paraneoplastic OMS was mostly associated with SCLC or breast cancer (Dropcho and Payne, 1986; Anderson *et al.*, 1988; Luque *et al.*, 1991). The other two patients had stomach and renal adenocarcinomas. As in other neurological paraneoplastic syndromes, OMS in adult patients has been occasionally associated with a wide variety of tumours: thyroid (Dropcho and Payne, 1986), melanoma (Berger and Mehari, 1999), pancreas (Aggarwal and Williams, 1997; Honnorat *et al.*, 1997), thymic carcinoma (Schwartz *et al*., 1990), gall bladder (Corcia *et al*., 1997), neurofibrosarcoma (Mitoma et *al*., 1996), chondrosarcoma (Kearsley *et al*., 1985) and Hodgkin's disease (Kay *et al*., 1993).

The clinical outcome of our paraneoplastic OMS patients was worse than that of idiopathic OMS patients despite treatment with immunotherapy. Only one of our patients had a complete recovery from the OMS before the tumour was diagnosed and treated. Although this good evolution has been observed previously (Anderson *et al*., 1988; Furman *et al.*, 1988; Das *et al.*, 1999), the majority of patients with paraneoplastic OMS had only a partial recovery and some died due to the evolution of the OMS to severe encephalopathy and coma within a few weeks if immunotherapy was not associated with treatment of the tumour. Our observation emphasizes the importance of early diagnosis and treatment of the underlying cancer in these patients and agrees with that shown in other neurological paraneoplastic syndromes (Chalk *et al*., 1990; Keime-Guibert *et al*., 1999) where effective treatment of the cancer, usually a SCLC as in OMS, is important to control the neurological dysfunction. Despite the key value of the antineoplastic treatment, the use of immunotherapy should be considered in the management of paraneoplastic OMS because isolated case reports have shown a beneficial effect of corticosteroids (Pranzatelli, 1992), protein A column immunoadsorption (Nitschke *et al*., 1995) and IVIG (Petruzzi and de Alarcon, 1995; Das *et al*., 1999). In addition, immunotherapy may prevent further progression (see Cases 16 and 24) until the tumour is treated.

The cause of neither idiopathic nor of paraneoplastic OMS is known. However, the response to immunotherapy in some cases and the presence of mild but widespread CNS lymphocytic infiltrates in the autopsy studies suggest an autoimmune pathogenesis (Pranzatelli, 1992). Unlike OMS in children (Connolly *et al.*, 1997) or other neurological paraneoplastic syndromes (Dalmau and Posner, 1999), specific antineuronal antibodies are not found in patients with idiopathic or paraneoplastic OMS, with the exception of the anti-Ri antibody in patients with OMS and gynaecological cancer (Luque *et al*., 1991) and isolated case reports (Hersh *et al.*, 1994; Honnorat *et al.*, 1997). One of our patients with OMS and SCLC presented anti-amphiphysin and low titres of anti-Hu antibodies. Both antibodies may be seen in a minority of patients with SCLC without neurological

disorders (Dalmau *et al*., 1990; Saiz *et al*., 1999) and the possibility of a coincidental finding cannot be ruled out. Interestingly, only one of the two patients with OMS and breast cancer had anti-Ri antibodies. These antibodies have been described in patients with OMS and no cancer (Hormigo *et al*., 1994) and our observation suggests the absence of anti-Ri antibodies does not rule out the possibility of an underlying gynaecological cancer in a patient with OMS (Scholz *et al.*, 1994).

OMS shares some features with LEMS and neuromyotonia: the absence of neuronal loss and the possibility of clinical remissions. Both disorders are caused by an autoimmune attack against cell surface antigens (Lang and Vincent, 1996), therefore, a similar mechanism for OMS could be implicated. Antibodies to VGCC are present in the serum of up to 7% of patients with paraneoplastic disorders of the central nervous system (Voltz *et al*., 1999), particularly cerebellar degeneration where they were found in 16% of patients, some of them without clinical evidence of LEMS (Mason *et al*., 1997). The present study shows anti-VGCC antibodies are not associated with OMS. The presence of antibodies against other channel types or membrane receptors that interfere with the normal physiology of the neurone should be evaluated in future studies.

In conclusion, idiopathic and paraneoplastic OMS have different clinical courses. Idiopathic OMS presents an age-dependent prognosis and immunotherapy seems to be associated with a faster recovery. By contrast, paraneoplastic OMS may be a life-threatening condition, particularly if the underlying malignancy is not discovered and treated. The currently known anti-neuronal antibodies are not consistently found in OMS but when present they favour a paraneoplastic origin.

Acknowledgements

We wish to thank Dr Dalmau for his critical review of the manuscript and Mrs Mercé Bonastre for her excellent technical support. This study was supported in part by grant SGR 9500027 Generalitat de Catalunya, Spain (F.G.).

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Received July 5, 2000. Revised October 10, 2000.
Accepted October 23, 2000.