Original Investigation

Clinical and Immunological Features of Opsoclonus-Myoclonus Syndrome in the Era of Neuronal Cell Surface Antibodies

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IMPORTANCE Most studies on opsoclonus-myoclonus syndrome (OMS) in adults are based on small case series before the era of neuronal cell surface antibody discovery.

OBJECTIVE To report the clinical and immunological features of idiopathic OMS (I-OMS) and paraneoplastic OMS (P-OMS), the occurrence of antibodies to cell surface antigens, and the discovery of a novel cell surface epitope.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study and laboratory investigations of 114 adult patients with OMS at a center for autoimmune neurological disorders done between January 2013 and September 2015.

MAIN OUTCOMES AND MEASURES Review of clinical records. Immunohistochemistry on rat brain and cultured neurons as well as cell-based assays were used to identify known autoantibodies. Immunoprecipitation and mass spectrometry were used to characterize novel antigens.

RESULTS Of the 114 patients (62 [54%] female; median age, 45 years; interquartile range, 32-60 years), 45 (39%) had P-OMS and 69 (61%) had I-OMS. In patients with P-OMS, the associated tumors included lung cancer (n = 19), breast cancer (n = 10), other cancers (n = 5), and ovarian teratoma (n = 8); 3 additional patients without detectable cancer were considered to have P-OMS because they had positive results for onconeuronal antibodies. Patients with I-OMS, compared with those who had P-OMS, were younger (median age, 38 [interquartile range, 31-50] vs 54 [interquartile range, 45-65] years; *P* < .001), presented more often with prodromal symptoms or active infection (33% vs 13%; *P* = .02), less frequently had encephalopathy (10% vs 29%; *P* = .01), and had better outcome (defined by a modified Rankin Scale score ≤2 at last visit; 84% vs 39%; *P* < .001) with fewer relapses (7% vs 24%; *P* = .04). Onconeuronal antibodies occurred in 13 patients (11%), mostly Ri/ANNA2 antibodies, which were detected in 7 of 10 patients (70%) with breast cancer. Neuronal surface antibodies were identified in 12 patients (11%), mainly glycine receptor antibodies (9 cases), which predominated in P-OMS with lung cancer (21% vs 5% in patients with OMS without lung cancer; *P* = .02); however, a similar frequency of glycine receptor antibodies was found in patients with lung cancer without OMS (13 of 65 patients [20%]). A novel cell surface epitope, human natural killer 1 (HNK-1), was the target of the antibodies in 3 patients with lung cancer and P-OMS.

CONCLUSIONS AND RELEVANCE Patients with I-OMS responded better to treatment and had fewer relapses than those with P-OMS. Older age and encephalopathy, significantly associated with P-OMS, are clinical clues suggesting an underlying tumor. Glycine receptor antibodies occur frequently in P-OMS with lung cancer, but the sensitivity and specificity are low. The HNK-1 epitope is a novel epitope in a subset of patients with P-OMS and lung cancer.

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O psoclonus-myoclonus syndrome (OMS) is character-
ized by the combination of opsoclonus and arrhyth-
mic action myoclonus that predominantly involves
trunk and limbs usually accompanied by axial ataxia and
dysarthria.[1] The 2 most common causes of OMS are paraneo-
plastic and idiopathic,[2,3] but the clinical features, types of tu-
mors, and other comorbidities are different in children and
adults. The current study examines these in adults.[4]

Several clinical and laboratory findings suggest that para-
neoplastic OMS (P-OMS) and idiopathic OMS (I-OMS) are im-
mune mediated.[5] The symptom presentation is usually acute
or subacute, the presence of pleocytosis is common, and pa-
tients often respond to immunotherapy. Autopsy studies may
show mild perivascular lymphocytic cuffs but rarely demon-
strate neuronal degeneration or extensive T-cell infiltrates, sug-
gesting that the disorder could be mediated by antibodies rather
than cytotoxic T-cell mechanisms.[6,7]

To our knowledge, with the exception of Ri/ANNA2 anti-
bodies in patients with OMS and breast cancer, the search for
other antibodies specific for OMS has not revealed a common
biomarker of the disease.[8,9] Most of these studies were done
before the discovery of antibodies to neuronal cell surface pro-
teins that currently characterize many types of autoimmune
encephalitis.[10] Therefore, a systematic analysis of these anti-
bodies in adult OMS has not been done. Recently, antibodies
to dendritic surface antigens were detected in 10% of pa-
tients with adult and pediatric OMS but the target antigen was
not identified.[11] In the current study, we examine a large se-
ries of adult patients with P-OMS or I-OMS to define clinical
and immunological subtypes of OMS, including possible as-
sociations with neuronal cell surface antibodies, and to de-
scribe a novel paraneoplastic epitope.

Methods

Patients

One hundred fourteen patients with OMS whose serum and
cerebrospinal fluid (CSF) samples were sent for antibody test-
ing to the laboratories of Hospital Clínic, Barcelona, Spain, or
the University of Pennsylvania, Philadelphia, between Janu-
ary 1995 and December 2014 were included in the study, which
was conducted between January 2013 and September 2015.
Samples from the University of Pennsylvania used in a recent
study were not included.[11] Inclusion criteria were the follow-
ing: (1) aged 18 years or older; (2) adequate clinical informa-
tion; (3) paraneoplastic, idiopathic, or infectious causes of OMS,
and exclusion of structural, toxic, and metabolic causes; and
(4) serum or CSF sample available for antibody testing. Clini-
cal information was obtained by us or provided by the refer-
ring physicians through a written questionnaire, telephone
interviews, or review of medical records. The OMS was con-
sidered P-OMS when a tumor was diagnosed within 5 years of
onset of the neurological symptoms or when onconeuronal an-
tibodies were identified.[12]

Written informed consent for the storage and use of
samples for research was obtained from patients or representa-
tive family members. The study was approved by the insti-

Key Points

Question: Are there clinical clues or antibody biomarkers that
differentiate idiopathic from paraneoplastic
opsoclonus-myoclonus syndrome (OMS)?

Results: In this cohort study, older age and encephalopathy were
significantly associated with paraneoplastic OMS, and
paraneoplastic OMS and being older than 40 years were
independently associated with poor outcome. Neuronal surface
antibodies were identified in 12 patients (11%), mainly glycine
receptor antibodies, which predominated in paraneoplastic OMS
with lung cancer.

Meaning: Patients with idiopathic OMS had better outcomes than
those with paraneoplastic OMS.

tutional review boards of the University of Pennsylvania and
Hospital Clínic, Barcelona.

Detection of Antineuronal Antibodies and Screening for Novel Cell Surface Autoantigens

All serum and CSF samples (70 paired samples, 39 serum
samples, and 5 CSF samples) were examined for onconeural
antibodies (Hu, Yo, Ri, CRMP5, amphiphysin, Ma2, Tr, and
Zic4), glutamic acid decarboxylase (GAD), and cell surface
antibodies (N-methyl-D-aspartate receptor [NMDAR],
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
receptor [AMPAR], γ-aminobutyric acid type A receptor
[GABA$_A$R], γ-aminobutyric acid type B receptor [GABA$_B$R],
glycine receptor [GlyR], contactin-associated protein 2
[CASPR2], leucine-rich glioma-inactivated protein 1 [LGI1], di-
peptidyl-peptidase-like protein-6 [DPPX], metabotropic
glutamate receptor 1 [mGluR1], and metabotropic glutamate
receptor 5 [mGluR5]) using previously reported techniques.[13-17]
Samples were also examined for IgG and IgM antibodies to
unknown cell surface antigens using a combination of
techniques (tissue immunohistochemistry, cell-based as-
says, cultured live neurons) and the novel autoantigens
precipitated, as reported.[13,14] All techniques are explained in
detail in the eAppendix in the Supplement.

To determine the relevance of GlyR antibodies in pa-
tients with OMS, serum samples of 254 controls (30 healthy
individuals, 20 with neurodegenerative disorders, 55 with mul-
tiple sclerosis, 55 with autoimmune encephalitis with anti-
bodies against surface antigens, 65 with lung cancer, and 29
with paraneoplastic neurological syndromes [PNSs] other than
OMS associated with lung cancer) were used as controls. Hu-
man natural killer 1 (HNK-1) antibodies were investigated by
immunohistochemistry (eAppendix in the Supplement) in the
CSF samples of 20 patients with lung cancer and PNSs other
than OMS.

Statistical Analysis

Demographic information and clinical and immunological fea-
tures comparing P-OMS and I-OMS were analyzed with Fisher
exact test, χ^2 test, or Mann-Whitney U test when appropriate.
Outcome analysis was only considered in patients with at least
3 months of follow-up and was assessed with the modified
Rankin Scale (mRS).[15] Patients were considered to have a good

Table. Clinical Features of Patients With P-OMS and I-OMS

| Characteristic | No. (%) | | P Value |
	P-OMS (n = 45)	I-OMS (n = 69)	
Age, median (IQR), y	54 (45-65)[a]	38 (31-50)	<.001
Female	24 (53)	38 (55)	.86
Prodromal and/or infection	6 (13)	23 (33)	.02
Autoimmune background	3 (7)	11 (16)	.14
Presenting symptoms			
Acute vertigo	22 (49)	47 (68)	.04
Subacute ataxia or myoclonus	11 (24)	8 (12)	.07
Other symptoms[b]	12 (27)	14 (20)	.43
Additional symptoms at any time			
Encephalopathy	13 (29)	7 (10)	.01
Cranial nerve palsy	7 (16)	4 (5)	.02
Severe behavioral changes	6 (13)	4 (6)	.16
CSF studies (n = 90)	(n = 34)	(n = 56)	
Abnormal	24 (71)	42 (75)	.65
WBC count >5/µL	16 (47)	34 (61)	.21
Protein >45 mg/dL	14 (41)	18 (32)	.38
Follow-up, median (IQR), mo (n = 81)	(n = 38)	(n = 43)	
Duration, median (IQR), mo	14 (6-27)	20 (8-45)	.36
Poor outcome, mRS score >2[c]	23 (61)	7 (16)	<.001
OMS relapse	9 (24)	3 (7)	.04

Abbreviations: CSF, cerebrospinal fluid; I-OMS, idiopathic opsoclonus-myoclonus syndrome; IQR, interquartile range; mRS, Modified Rankin Scale; OMS, opsoclonus-myoclonus syndrome; P-OMS, paraneoplastic opsoclonus-myoclonus syndrome; WBC, white blood cell.

SI conversion factor: To convert WBC count to ×10^9 per liter, multiply by 0.001.

[a] Including 8 patients with ovarian teratoma who were much younger (median age, 23 years; IQR, 22-30 years).

[b] Other symptoms at presentation included 8 patients with abnormal behavior, 7 with encephalopathy, 5 with cranial nerve palsy, 3 with lower limb bilateral weakness, and 1 each with lower limb radiculopathic pain, cognitive deficits, and insomnia.

[c] Only patients with detailed information about treatment and follow-up longer than 3 months.

outcome if the mRS score at the last follow-up was 0 to 2 and a poor outcome if the mRS score was higher than 2. Factors influencing outcome were assessed by univariable binary logistic regression (eTable 1 in the Supplement). Factors associated with a poor outcome (P < .10) were included in a multivariable binary logistic regression model and approached by forward stepwise procedure; variables were considered independent when they remained statistically significant. Odds ratio with 95% confidence interval was used to measure the effect of independent variables. The 95% confidence interval for sensitivity and specificity of Ri antibodies for the diagnostic assessment of breast cancer was determined with the Wilson procedure. Stata version 13.1 statistical software (StataCorp LP) was used for the analyses.
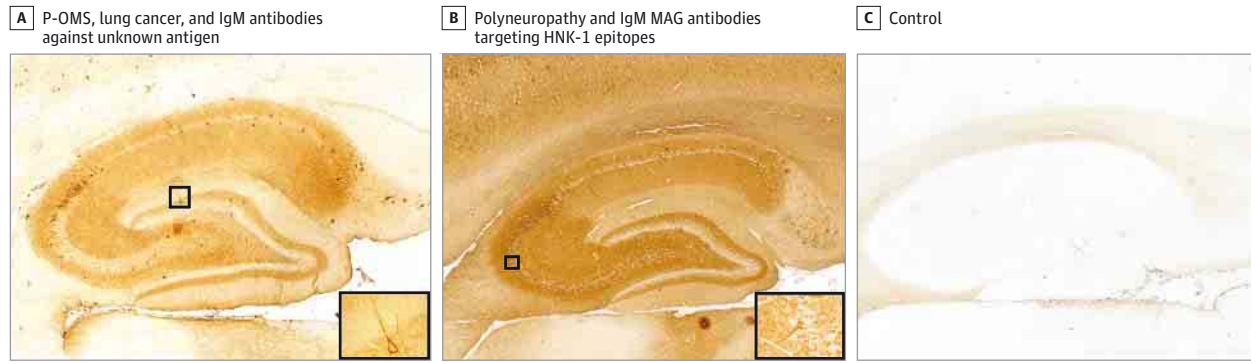
Results

Clinical Features

One hundred fourteen adults with OMS (62 female [54%]; median age, 45 years; interquartile range [IQR], 32-60 years) fulfilled the study criteria. Forty-five patients (39%) had P-OMS and 69 (61%) had I-OMS. Patients with P-OMS included 19 (5 women) with lung cancer (13 with small cell lung cancer [SCLC] and 6 with non-SCLC), 10 with breast cancer, 8 with ovarian teratoma, and 5 men with other cancer types (1 patient each: testicular seminoma, stomach, thymus, kidney, and oropharyngeal carcinoma). Three additional patients without detectable cancer were considered to have P-OMS because they had positive results for onconeuronal antibodies (Ri, CRMP5, or Ma2). Symptoms of OMS preceded the diagnosis of the tumor

in 29 of 42 patients (69%), with no differences among tumor types. Among the 13 patients whose tumor was diagnosed before onset of OMS, 4 developed the symptoms soon after tumor removal or biopsy, and another 3 developed the symptoms during chemotherapy. Onconeuronal antibodies were identified in 13 patients (11%) (Ri, 8; Ma2, 3; Zic4, 1; and CRMP5, 1). Seven of 10 patients (70%) with breast cancer harbored Ri antibodies (sensitivity, 70%; 95% CI, 40-89; specificity, 99%; 95% CI, 95-100). Other cancer types associated with onconeuronal antibodies were lung cancer (2 of 19 patients [11%]: 1 had Ma2 and the other Zic4 antibodies) and stomach cancer (1 patient with Ma2). The **Table** shows the clinical features of patients with I-OMS compared with those with P-OMS. Patients with I-OMS were younger than those with P-OMS (median age, 38 [IQR, 31-50] vs 54 [45-65] years; P < .001); however, the P-OMS group showed a bimodal age distribution: the group with ovarian teratoma was younger (median age, 23 years; IQR, 22-30 years) than those with I-OMS (P = .003), whereas the group with other tumors was older (median age, 60 years; IQR, 46-66 years; P < .001). Prodromal symptoms suggestive of viral infections or history of infection or of recent vaccinations were more frequent in patients with I-OMS (33% vs 13%; P = .02). Six patients with I-OMS, but none with P-OMS, had a confirmed active infection (4 with human immunodeficiency virus [HIV], 1 with hepatitis C virus, and 1 with tuberculosis). Acute vertigo with vomiting and/or gait instability was the most common symptom presentation in I-OMS or P-OMS, often leading to an initial misdiagnosis of peripheral vertigo. However, while patients with I-OMS were more likely than those with P-OMS to present with isolated vertigo (68% vs 49%; P = .04), patients with P-OMS more frequently had coexist-

Figure 1. Immunostaining Results on Frozen Sections of Rat Brain

A P-OMS, lung cancer, and IgM antibodies against unknown antigen

B Polyneuropathy and IgM MAG antibodies targeting HNK-1 epitopes

C Control

A-C, Immunoreactivity developed with standard avidin-biotin immunoperoxidase technique. A, Cerebrospinal fluid immunoreactivity from 1 of the 3 patients with paraneoplastic opsoclonus-myoclonus syndrome (P-OMS), lung cancer, and IgM antibodies against an unknown antigen (original magnification ×40). Inset, Higher-magnification image (original magnification ×400). B, This pattern of immunostaining was similar to that seen in patients with polyneuropathy and IgM myelin-associated glycoprotein (MAG) antibodies targeting glycosylated human natural killer 1 (HNK-1) epitopes. Note the high similarity in the staining surrounding the neuronal cell bodies and along proximal dendrites of large neurons (original magnification ×40). Inset, Higher-magnification image (original magnification ×400). C, The absence of reactivity in the cerebrospinal fluid of a control (original magnification ×40).

Figure 2. Immunoblot Results

Molecular Weight, kDa

148 —

98 —

64 —

1 2 3 4 5 6
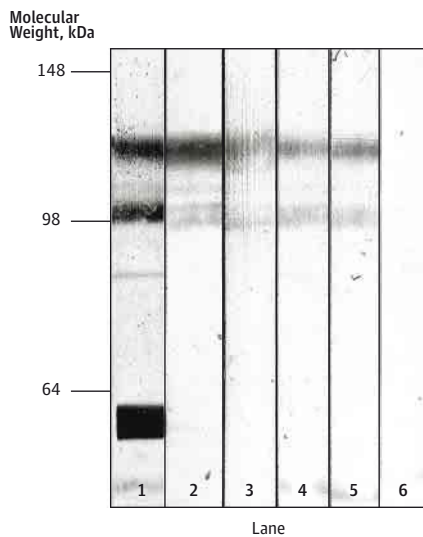
Lane

Immunoblot of human myelin proteins probed with serum of a patient with IgM myelin-associated glycoprotein antibodies and neuropathy (lane 1), a commercial antibody against human natural killer 1 (HNK-1) (lane 2), and the cerebrospinal fluid of our 3 patients with paraneoplastic opsoclonus-myoclonus syndrome and lung cancer (lanes 3-5). Note that all patient and commercial antibodies reacted with bands of similar molecular weight that are not shown by the negative control sample (lane 6).

ing or early development of encephalopathy (29% vs 10%; $P = .01$) and other symptoms, such as cranial nerve palsy (16% vs 5%; $P = .02$) (Table).

Detailed information regarding treatment and outcome was available for 81 patients (71%): 70 (86%) received immunotherapy and 11 (14%) did not. Among the 70 patients treated with immunotherapy, 27 (39%) received steroids, 10 (14%) received intravenous immunoglobulin (IVIg), 24 (34%) received steroids and IVIg, and 9 (13%) received steroids, IVIg, and plasma exchange. Six of these 70 patients also were treated with azathioprine (n = 4), rituximab (n = 1), or rituximab and mycophenolate mofetil (n = 1). At the last follow-up (median, 17 months; IQR, 6-33 months), 51 of 81 patients (63%) had a good outcome (36 complete or almost complete recovery [mRS score ≤2]) and 30 (37%) had a poor outcome (10 had an mRS score ≥3, 11 had an mRS score of 4 or 5, and 9 died). In multivariate analysis, independent factors significantly associated with a poor outcome adjusted by time of follow-up were being older than 40 years (odds ratio = 8.6; 95% CI, 1.9-38.4) and paraneoplastic origin (odds ratio = 6.9; 95% CI, 2.0-23.7). Twelve of 81 patients (15%) developed relapsing OMS; relapsing symptoms were more frequent in patients with P-OMS than in those with I-OMS (24% vs 7%; $P = .04$).
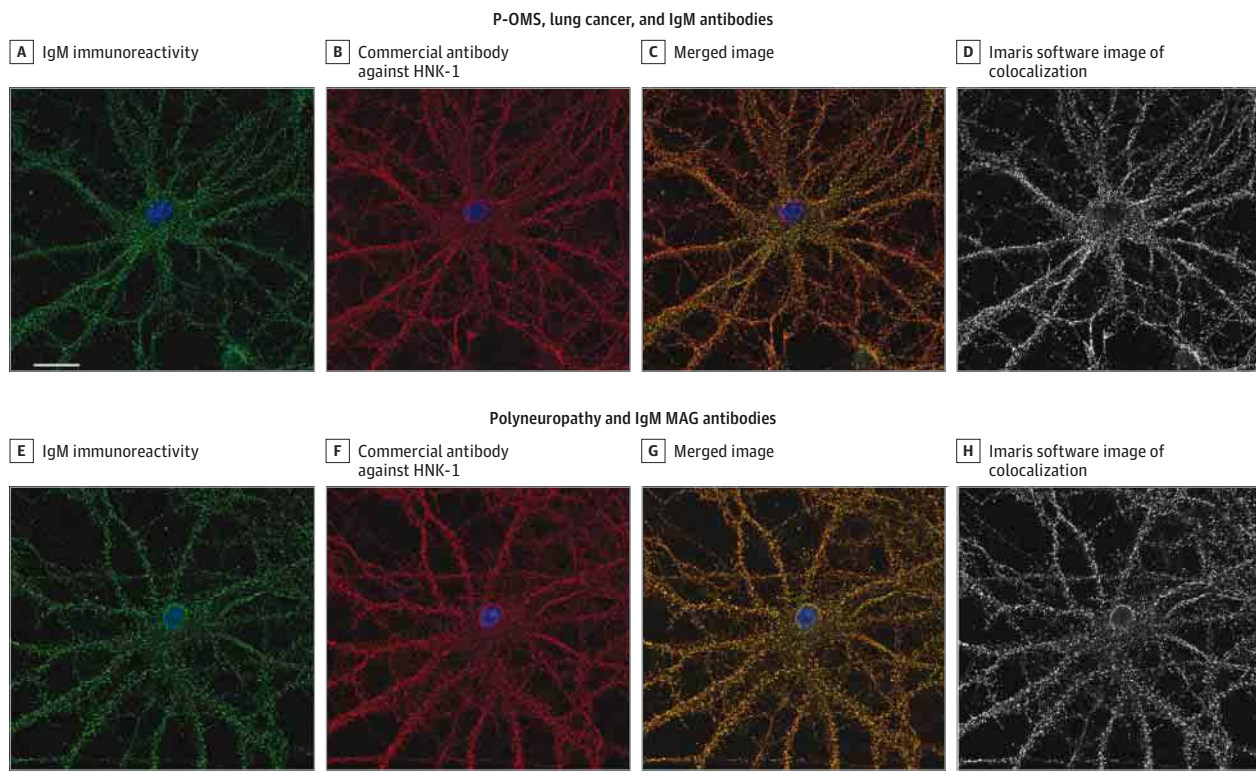
Antibodies to Known Neuronal Surface Antigens

Antibodies to known cell surface antigens were identified in the serum or CSF of 12 patients (11%), including 9 with antibodies to GlyR, 1 with antibodies to $GABA_BR$, 1 with antibodies to NMDAR, and 1 with antibodies to DPPX. The 2 patients with $GABA_BR$ or NMDAR antibodies were young women (in their mid-30s) who developed typical OMS; the patient with $GABA_BR$ antibodies was previously described.[16] The patient with NMDAR antibodies was found to have an ovarian teratoma and fully recovered after tumor removal and administration of IVIg, and steroids. The patient with DDPX antibodies was a man in his late 50s who during 1 year developed weight loss (22 kg), dizziness, ataxia, diplopia, tremor, opsoclonus, myoclonus, and downbeat nystagmus. He also had insomnia, major depressive symptoms, and mild cognitive deficits. Findings on magnetic resonance imaging of the brain and cervical spine as well as electroencephalography were normal. He received oral steroids without symptom improvement.

Figure 3. Immunofluorescence Results

P-OMS, lung cancer, and IgM antibodies

A IgM immunoreactivity
B Commercial antibody against HNK-1
C Merged image
D Imaris software image of colocalization

Polyneuropathy and IgM MAG antibodies

E IgM immunoreactivity
F Commercial antibody against HNK-1
G Merged image
H Imaris software image of colocalization

Immunofluorescence on live hippocampal neurons incubated with the cerebrospinal fluid of 1 of the 3 patients with paraneoplastic opsoclonus-myoclonus syndrome (P-OMS), lung cancer, and IgM antibodies (A-D) and the serum of a patient with polyneuropathy and IgM myelin-associated glycoprotein (MAG) antibodies (E-H). The punctate IgM immunoreactivity of the 2 patients (A and E) colocalized with the reactivity of a commercial antibody against human natural killer 1 (HNK-1) (B and F), shown in the merged images (C and G); a high degree of colocalization was confirmed by Imaris software (Mander coefficient = 0.8 for both fluorescent channels; the coefficient ranges from 0.0 [no colocalization] to 1.0 [full colocalization][19]) (D and H) (scale bar = 20 μm).

Among the 9 patients (8%) with GlyR antibodies (7 in serum, 1 in CSF, and 1 in both), 6 had cancer (4 had lung cancer, 1 had breast cancer, and 1 had testicular seminoma); 3 of the 9 patients with GlyR antibodies had coexisting onconeural antibodies (Ri, Zic4, and Ma2). Overall, GlyR antibodies were more frequently detected in patients with OMS and lung cancer (4 of 19 patients [21%]) vs patients with OMS without lung cancer (5 of 95 patients [5%]) (P = .02). However, patients with lung cancer without OMS (13 of 65 patients [20%]) or with other PNSs (3 of 29 patients [10%]) also frequently had GlyR antibodies (P = .45). Of the 160 controls without cancer, 8 (5%) had GlyR antibodies (4 with multiple sclerosis and 4 with classic anti-NMDAR encephalitis).

No patients with OMS had GABA$_A$R antibodies. The 2 previously described patients with these antibodies[17] were not included because the clinical and outcome information was very limited.

Antibodies to Novel Neuronal Surface Antigens

Studies on rat brain sections and live hippocampal neurons identified 7 patients with antibodies against novel neuronal cell surface antigens. In 4 patients, the antibodies were of the IgG class (3 had I-OMS and 1 had OMS with ovarian teratoma) and im-

munoprecipitation studies did not reveal the antigen. In the other 3 patients (2 with non-SCLC and 1 with SCLC, 2 of them with coexisting GAD antibodies) without monoclonal gammopathy or neuropathy, IgM antibodies in brain sections had an immunoreactivity identical to that observed with a commercial monoclonal antibody (Sigma-Aldrich) against the glycosylated HNK-1 epitope or the serum of patients with neuropathy, monoclonal gammopathy, and IgM antibodies against myelin-associated glycoprotein (MAG), a protein that contains the HNK-1 epitope (Figure 1).[18] The same results were obtained in immunoblots of an enriched extract of human myelin proteins (Figure 2). The specific HNK-1 reactivity of the 3 patients with IgM antibodies was confirmed in cultured live hippocampal neurons, which showed remarkable colocalization with the reactivity of the monoclonal HNK-1 antibody (Figure 3). Furthermore, immunoprecipitation studies using a mixed pool of CSF from the 3 patients consistently isolated sequences of glutamate receptor 2 (GluR2), a subunit of AMPAR known to contain the glycosylated HNK-1 epitope (20 peptides of GluR2 sequence, 21% of protein coverage; eFigure in the Supplement; Figure 4).[20] These findings reveal a subset of patients with P-OMS and antibodies targeting proteins with the HNK-1 epitope. None of the 20 controls with SCLC without OMS had CSF IgM HNK-1 antibodies.

Figure 4. Immunoblot Results of the Immunoprecipitated Proteins
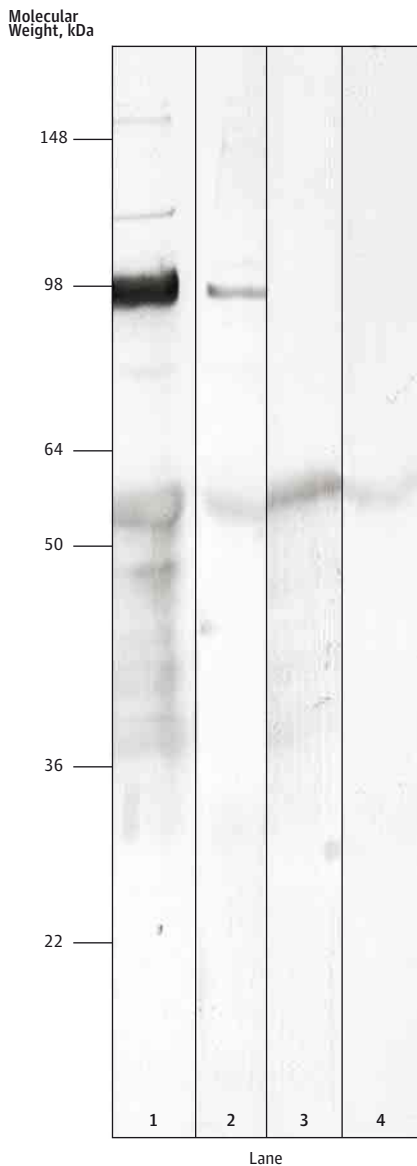
To determine whether the immunoprecipitated antigen was the glutamate receptor 2 (GluR2) subunit, immunoblots of neuronal proteins precipitated with cerebrospinal fluid from patients with paraneoplastic opsoclonus-myoclonus syndrome and IgM human natural killer 1 antibodies were probed with commercial antibodies against the GluR2 subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) (lane 1) and a monoclonal human natural killer 1 antibody (lane 2). Both antibodies recognize a similar band in the 98-kDa range consistent with GluR2. This band was not observed in immunoblots of neuronal proteins precipitated with a control's cerebrospinal fluid probed with the same antibodies against GluR2 (lane 3) and human natural killer 1 (lane 4).

Discussion

Our study represents the largest series, to our knowledge, of adult patients with OMS. The current findings along with those of previous studies[2,3,21-23] have several practical implications for the diagnosis and management of patients with this dis-

order. First, once toxic, metabolic, and structural causes of OMS are ruled out,[1] the most important indicator of paraneoplastic OMS is the patient's age. For adult patients younger than 40 years, the probability of an underlying tumor other than ovarian teratoma[23] is very low, suggesting that aggressive or periodic investigations for an occult cancer and the use of extensive panels of paraneoplastic antibodies are not necessary (with the exception of Ri antibodies in middle-aged women). Second, P-OMS should be considered in older patients who develop encephalopathy or symptoms beyond the classic picture of OMS. The current series confirms that lung cancer, particularly SCLC, is the most frequently involved tumor, followed by breast and gynecological cancers.[2,3] Third, whereas Ri/ANNA2 antibodies are good predictors of P-OMS related to breast cancer, other paraneoplastic antibodies are rare or not consistently found in P-OMS.[2,3,9] In the present study, GlyR antibodies occurred in 21% of patients with lung cancer–related P-OMS, but the sensitivity and specificity were not robust enough to suggest the use of these antibodies as biomarkers of P-OMS. Fourth, compared with I-OMS, patients with P-OMS had more relapses and worse outcome, confirming our findings in a smaller previous series of patients.[2] These results emphasize the need for tumor treatment and up-front use of more aggressive immunotherapies such as rituximab or intravenous cyclophosphamide to treat P-OMS.

In adults younger than 40 years, the most likely cause of OMS is idiopathic or parainfectious, both of which have a better prognosis than P-OMS or than OMS in children.[24,25] First-line immunotherapies, such as steroids, IVIg, or plasma exchange, are associated with good outcome in most of these patients who usually receive 1 or several types of symptomatic therapy (topiramate,[26] gabapentin,[27] or benzodiazepines[28]; not investigated in the current study). Antineuronal antibodies are usually negative, although a few exceptions have been reported (summarized in eTable 2 in the Supplement).[29-31] In this age group, it is important to exclude an underlying ovarian teratoma or HIV infection,[23,32] which in the current series occurred in 12 of 70 patients younger than 40 years (17%). Patients with ovarian teratoma frequently develop additional symptoms, such as dysautonomia, behavioral change, or drowsiness, and results of testing for NMDAR antibodies are almost always negative.[23] Although we identified a patient with OMS, ovarian teratoma, and NMDAR antibodies, the 3 previously reported cases (one of them a young child) with OMS and NMDAR antibodies had typical symptoms of anti-NMDAR encephalitis.[33-35] Also, OMS may be the initial manifestation of HIV infection or may occur during immune reconstitution at the onset of antiretroviral therapy.[36,37] There are no clinical features characteristic of HIV-related OMS; therefore, a high degree of awareness is needed for not missing this diagnosis.[32,38,39]

Glycine receptor antibodies were more frequent in P-OMS (mainly associated with SCLC) than in other forms of OMS. This finding is interesting because glycine is the neurotransmitter of omnipause neurons in the paramedian pontine reticular formation that exert a tonic inhibition of saccadic burst neurons.[40,41] These antibodies were initially detected in pa-

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tients with progressive encephalomyelitis with rigidity and myoclonus.[42] Symptoms of progressive encephalomyelitis with rigidity and myoclonus, like those of OMS, are believed to result from a disturbance of the inhibitory (glycine/GABAergic) circuits, which would be altered by GlyR antibodies.[42] However, GlyR antibodies were not found in a previous report that studied 4 patients with I-OMS.[43] The presence of GlyR antibodies in our patients was unlikely related to OMS. Indeed, these antibodies have been reported (mainly in serum) in subgroups of patients with optic neuritis,[44] GAD antibody–associated stiff person syndrome or cerebellar ataxia,[45] and multiple sclerosis,[44] suggesting that in some patients they may reflect a non–syndrome-specific immune activation, or propensity to autoimmunity. An alternative explanation is that GlyR antibodies may reflect the presence of a tumor; this is supported by a similar frequency of these antibodies in patients with SCLC without OMS or with other PNSs, and the expression of the α1 subunit of the GlyR in SCLC cell lines.[46]

We detected IgM antibodies against the carbohydrate epitope HNK-1 in the CSF of 3 patients with P-OMS and lung cancer. The HNK-1 epitope is the main target epitope of IgM antibodies against MAG in patients with neuropathy and IgM monoclonal gammopathy[18] and, to our knowledge, HNK-1 has not been previously reported as an autoantigen in other neurological disorders. This epitope has been previously reported in membrane proteins of cell lines and biopsies of SCLC.[47,48] In brain, HNK-1 is present not only in MAG but also in several proteins such as cell adhesion molecules, tenas-

cins, and integrins widely present in the brain.[49,50] These proteins as well as the HNK-1-containing GluR2 subunit of AMPAR, which was precipitated with the CSF of our patients, are involved in synaptic plasticity and a variety of neuronal functions.[20]

Conclusions

Our findings show that OMS in adults is the common manifestation of different disorders associated with distinct comorbidities (cancer, teratoma, idiopathic, inflammation, infection) and a variety of paraneoplastic and cell surface autoantibodies that were collectively detected in only 19% of the patients (10 patients with onconeural antibodies, 9 with antibodies to known cell surface antigens, and 3 with both types of antibodies). Future studies aiming to identify immunological mechanisms in OMS should focus on methods different from those used in autoimmune encephalitis and cell surface antigens. Although unknown antibodies may still be involved, as shown here in 3 patients, an impairment of synaptic signaling by other mechanisms, perhaps circulating inflammatory molecules, should be considered. Electrophysiological assessment of neuronal cultures or acute slices of brain exposed to patients' serum or CSF may shed light on the type of molecular targets involved. Meanwhile, the clinical profile of OMS suggests an immune-mediated pathogenesis. Immunotherapy should be considered despite the fact that no antibody markers are identified in most patients.

REFERENCES

1. Caviness JN, Forsyth PA, Layton DD, McPhee TJ. The movement disorder of adult opsoclonus. *Mov Disord*. 1995;10(1):22-27.

2. Bataller L, Graus F, Saiz A, Vilchez JJ; Spanish Opsoclonus-Myoclonus Study Group. Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. *Brain*. 2001;124(pt 2):437-443.

3. Klaas JP, Ahlskog JE, Pittock SJ, et al. Adult-onset opsoclonus-myoclonus syndrome. *Arch Neurol*. 2012;69(12):1598-1607.

4. Pike M. Opsoclonus-myoclonus syndrome. *Handb Clin Neurol*. 2013;112:1209-1211.

5. Pranzatelli MR. The immunopharmacology of the opsoclonus-myoclonus syndrome. *Clin Neuropharmacol*. 1996;19(1):1-47.

6. Ridley A, Kennard C, Scholtz CL, Büttner-Ennever JA, Summers B, Turnbull A. Omnipause neurons in two cases of opsoclonus associated with oat cell carcinoma of the lung. *Brain*. 1987;110(pt 6):1699-1709.

7. Young CA, MacKenzie JM, Chadwick DW, Williams IR. Opsoclonus-myoclonus syndrome: an autopsy study of three cases. *Eur J Med*. 1993;2(4):239-241.

8. Bataller L, Rosenfeld MR, Graus F, Vilchez JJ, Cheung NK, Dalmau J. Autoantigen diversity in the opsoclonus-myoclonus syndrome. *Ann Neurol*. 2003;53(3):347-353.

9. Luque FA, Furneaux HM, Ferziger R, et al. Anti-Ri: an antibody associated with paraneoplastic opsoclonus and breast cancer. *Ann Neurol*. 1991;29(3):241-251.

10. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. *Ann N Y Acad Sci*. 2015;1338:94-114.

11. Panzer JA, Anand R, Dalmau J, Lynch DR. Antibodies to dendritic neuronal surface antigens in opsoclonus myoclonus ataxia syndrome. *J Neuroimmunol*. 2015;286:86-92.

12. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for

paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75(8):1135-1140.

13. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol*. 2011;10(1):63-74.

14. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol*. 2010;9(1):67-76.

15. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604-607.

16. DeFelipe-Mimbrera A, Masjuan J, Corral Í, Villar LM, Graus F, García-Barragán N. Opsoclonus-myoclonus syndrome and limbic encephalitis associated with GABAB receptor antibodies in CSF. *J Neuroimmunol*. 2014;272(1-2):91-93.

17. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol*. 2014;13(3):276-286.

18. Ilyas AA, Quarles RH, MacIntosh TD, et al. IgM in a human neuropathy related to paraproteinemia binds to a carbohydrate determinant in the myelin-associated glycoprotein and to a ganglioside. *Proc Natl Acad Sci U S A*. 1984;81(4):1225-1229.

19. McDonald JH, Dunn KW. Statistical tests for measures of colocalization in biological microscopy. *J Microsc*. 2013;252(3):295-302.

20. Takeuchi Y, Morise J, Morita I, Takematsu H, Oka S. Role of site-specific N-glycans expressed on GluA2 in the regulation of cell surface expression of AMPA-type glutamate receptors. *PLoS One*. 2015;10(8):e0135644.

21. Anderson NE, Budde-Steffen C, Rosenblum MK, et al. Opsoclonus, myoclonus, ataxia, and encephalopathy in adults with cancer: a distinct paraneoplastic syndrome. *Medicine (Baltimore)*. 1988;67(2):100-109.

22. Digre KB. Opsoclonus in adults: report of three cases and review of the literature. *Arch Neurol*. 1986;43(11):1165-1175.

23. Armangue T, Titulaer MJ, Sabater L, et al. A novel treatment-responsive encephalitis with frequent opsoclonus and teratoma. *Ann Neurol*. 2014;75(3):435-441.

24. Matthay KK, Blaes F, Hero B, et al. Opsoclonus myoclonus syndrome in neuroblastoma: a report from a workshop on the dancing eyes syndrome at the advances in neuroblastoma meeting in Genoa, Italy, 2004. *Cancer Lett*. 2005;228(1-2):275-282.

25. De Grandis E, Parodi S, Conte M, et al. Long-term follow-up of neuroblastoma-associated opsoclonus-myoclonus-ataxia syndrome. *Neuropediatrics*. 2009;40(3):103-111.

26. Fernandes TD, Bazan R, Betting LE, da Rocha FC. Topiramate effect in opsoclonus-myoclonus-ataxia syndrome. *Arch Neurol*. 2012;69(1):133.

27. Moretti R, Torre P, Antonello RM, Nasuelli D, Cazzato G. Opsoclonus-myoclonus syndrome: gabapentin as a new therapeutic proposal. *Eur J Neurol*. 2000;7(4):455-456.

28. Bartos A. Effective high-dose clonazepam treatment in two patients with opsoclonus and myoclonus: GABAergic hypothesis. *Eur Neurol*. 2006;56(4):240-242.

29. Ariño H, Höftberger R, Gresa-Arribas N, et al. Paraneoplastic neurological syndromes and glutamic acid decarboxylase antibodies. *JAMA Neurol*. 2015;72(8):874-881.

30. Candler PM, Dale RC, Griffin S, et al. Post-streptococcal opsoclonus-myoclonus syndrome associated with anti-neuroleukin antibodies. *J Neurol Neurosurg Psychiatry*. 2006;77(4):507-512.

31. Morales-Briceño H, Rodríguez-Violante M, Cervantes-Arriaga A, Irani SR, Lees AJ, Silveira-Moriyama L. Opsoclonus myoclonus syndrome associated with GQ1b antibodies. *Mov Disord*. 2012;27(13):1615-1616.

32. Scott KM, Parker F, Heckmann JM. Opsoclonus-myoclonus syndrome and HIV-infection. *J Neurol Sci*. 2009;284(1-2):192-195.

33. Smith JH, Dhamija R, Moseley BD, et al. N-methyl-D-aspartate receptor autoimmune encephalitis presenting with opsoclonus-myoclonus: treatment response to plasmapheresis. *Arch Neurol*. 2011;68(8):1069-1072.

34. Kurian M, Lalive PH, Dalmau JO, Horvath J. Opsoclonus-myoclonus syndrome in anti-N-methyl-D-aspartate receptor encephalitis. *Arch Neurol*. 2010;67(1):118-121.

35. Player B, Harmelink M, Bordini B, Weisgerber M, Girolami M, Croix M. Pediatric opsoclonus-myoclonus-ataxia syndrome associated with anti-N-methyl-D-aspartate receptor encephalitis. *Pediatr Neurol*. 2015;53(5):456-458.

36. van Toorn R, Rabie H, Warwick JM. Opsoclonus-myoclonus in an HIV-infected child on antiretroviral therapy: possible immune reconstitution inflammatory syndrome. *Eur J Paediatr Neurol*. 2005;9(6):423-426.

37. Kanjanasut N, Phanthumchinda K, Bhidayasiri R. HIV-related opsoclonus-myoclonus-ataxia syndrome: report on two cases. *Clin Neurol Neurosurg*. 2010;112(7):572-574.

38. Ayarza A, Parisi V, Altclas J, et al. Opsoclonus-myoclonus-ataxia syndrome and HIV seroconversion. *J Neurol*. 2009;256(6):1024-1025.

39. Wiersinga WJ, Prins JM, van de Beek D. Therapy-resistant opsoclonus-myoclonus syndrome secondary to HIV-1 infection. *Clin Infect Dis*. 2012;54(3):447-448.

40. Lynch JW. Native glycine receptor subtypes and their physiological roles. *Neuropharmacology*. 2009;56(1):303-309.

41. Horn AK, Büttner-Ennever JA, Wahle P, Reichenberger I. Neurotransmitter profile of saccadic omnipause neurons in nucleus raphe interpositus. *J Neurosci*. 1994;14(4):2032-2046.

42. Carvajal-González A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain*. 2014;137(pt 8):2178-2192.

43. Iizuka T, Leite MI, Lang B, et al. Glycine receptor antibodies are detected in progressive encephalomyelitis with rigidity and myoclonus (PERM) but not in saccadic oscillations. *J Neurol*. 2012;259(8):1566-1573.

44. Martinez-Hernandez E, Sepulveda M, Rostásy K, et al. Antibodies to aquaporin 4, myelin-oligodendrocyte glycoprotein, and the glycine receptor α1 subunit in patients with isolated optic neuritis. *JAMA Neurol*. 2015;72(2):187-193.

45. Ariño H, Gresa-Arribas N, Blanco Y, et al. Cerebellar ataxia and glutamic acid decarboxylase antibodies: immunologic profile and long-term effect of immunotherapy. *JAMA Neurol*. 2014;71(8):1009-1016.

46. Gurrola-Diaz C, Lacroix J, Dihlmann S, Becker CM, von Knebel Doeberitz M. Reduced expression of the neuron restrictive silencer factor permits transcription of glycine receptor alpha1 subunit in small-cell lung cancer cells. *Oncogene*. 2003;22(36):5636-5645.

47. Hozumi I, Sato S, Tunoda H, et al. Shared carbohydrate antigenic determinant between the myelin-associated glycoprotein (MAG) and lung cancers: an immunohistochemical study by an anti-MAG IgM monoclonal antibody. *J Neuroimmunol*. 1987;15(2):147-157.

48. Willison HJ, Minna JD, Brady RO, Quarles RH. Glycoconjugates in nervous tissue and small cell lung cancer share immunologically cross-reactive carbohydrate determinants. *J Neuroimmunol*. 1986;10(4):353-365.

49. Matà S, Ambrosini S, Mello T, Lolli F, Minciacchi D. Anti-myelin associated glycoprotein antibodies recognize HNK-1 epitope on CNS. *J Neuroimmunol*. 2011;236(1-2):99-105.

50. Kizuka Y, Oka S. Regulated expression and neural functions of human natural killer-1 (HNK-1) carbohydrate. *Cell Mol Life Sci*. 2012;69(24):4135-4147.