Absence of GluD2 Antibodies in Patients With Opsoclonus-Myoclonus Syndrome

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Neurology® 2021;96:e1082-e1087. doi:10.1212/WNL.00000000000011410

Abstract

Objective

A recent study showed glutamate receptor delta 2 antibodies (GluD2-ab) in sera of patients with opsoclonus-myoclonus syndrome (OMS). Inconsistencies between cerebellar immunoreactivity and expression of GluD2 led us to hypothesize that these antibodies are not biomarkers of OMS.

Methods

Serum of 45 children with OMS (10 [22%] with neuroblastoma), 158 adults with OMS (53 [34%] with tumors), and 172 controls including 134 patients with several types of neurologic disorders, 18 with neuroblastoma without OMS, and 20 healthy participants were investigated. Antibodies were determined with 3 different techniques: (1) rat brain immunohistochemistry, (2) a live cell-based assay using a standard secondary antibody (2-step CBA), and (3) a similar CBA with a secondary and tertiary antibodies (3-step CBA). Two plasmids were used in the CBA studies. Three commercial GluD2-ab and 2 human sera with GluD2-ab served as controls for expression of GluD2.

Results

The 3 commercial GluD2-ab showed predominant reactivity with the molecular and Purkinje cell layers (where GluD2 is highly enriched), and were also positive with the indicated CBAs. Substantially milder reactivity with brain tissue and CBA was obtained with the 2 control human sera containing GluD2-ab. None of the 203 patients with OMS and 172 controls showed immunoreactivities consistent with GluD2-abs. Compared with a standard 2-step CBA, the 3-step assay did not improve antibody detection and showed more frequent nonspecific reactivity that was not immunoabsorbed with GluD2.

Conclusion

We did not find GluD2-ab in a large cohort of patients with OMS. GluD2-ab should not be considered diagnostic biomarkers of OMS.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

CBA = cell-based assay; **GluD2** = glutamate receptor delta 2; **GluD2-ab** = glutamate receptor delta 2 antibody; **IgG** = immunoglobulin G; **OMS** = opsoclonus-myoclonus syndrome; **RT** = room temperature.

Opsoclonus-myoclonus syndrome (OMS) is an eye movement disorder that in most patients is suspected to be autoimmune. Over the years, several autoantibodies have been reported in small subsets of patients, but most patients are neural antibody-negative.¹ In a recent study focused on patients with pediatric OMS and neuroblastoma, the authors hypothesized an advantage to using prenatal cerebellar rat tissue in order to immunoprecipitate the antigens.² Using this approach, the glutamate receptor delta 2 (GluD2) and other proteins were precipitated, and GluD2 was subsequently expressed in a cell-based assay (CBA) for GluD2 antibody (GluD2-ab) testing in patient sera. These studies showed that 14 of 16 children with OMS (87.5%) had GluD2-ab, suggesting that these antibodies could be used as biomarkers of OMS. However, 2 of 4 patients with neuroblastoma but without OMS (50%) were also antibody-positive.² Although the authors emphasized that selection of patients' sera and cerebellar tissue from very young rats (equivalent to 18–24 human months) were critical for antigen precipitation, the sera were selected based on their strong immunoreactivity with the granular cell layer and deep nuclei of adult rat cerebellum.² Moreover, the reported cerebellar immunoreactivity did not correspond with the characteristic pattern of expression of GluD2, which is highly enriched in the molecular layer and Purkinje cells of cerebellum.^{3,4} These findings led us to hypothesize that GluD2 is not a common autoantigen of OMS, and therefore, GluD2-ab testing is not useful for the diagnosis of this disease. Here we tested this hypothesis with 203 OMS patients and 172 controls.

Methods

Serum samples from 45 children with OMS (10 [22%] with neuroblastoma) and 158 adults with OMS (53 [34%] with tumors) sent for antibody testing to the laboratories of Hospital Clinic-IDIBAPS, Barcelona, Spain, or the University of Pennsylvania, Philadelphia, between 1992 and 2018, were investigated. General clinical features of most adults with OMS (136) had been previously reported.¹ Control serum samples (total 172) included 57 children and 115 adults with the following (distribution, children/adults): 18 neuroblastoma without OMS (18/0), 12 new-onset epilepsy (12/0), 24 multiple sclerosis (0/24), 24 Hashimoto encephalopathy (4/20), 16 autoimmune cerebellitis (5/11), 14 Rasmussen encephalitis (7/7), 15 autoimmune encephalitis with well-defined neuronal surface antibodies (4/11), 10 neuromyelitis optica spectrum disorders (0/10), 7 anti-Hu syndromes (0/7), 6 encephalitis with antibodies against unknown neuronal surface antigens (1/5), 6 MOG-antibody-associated syndromes (6/0), and 20 healthy blood donors (0/20). Clinical information was obtained by us or provided by the referring physicians through a written questionnaire or review of medical records.

Immunohistochemistry With Rat Brain

This technique has been previously reported.⁵ For this study, we used patients' or control serum samples (diluted 1:200) and 3 commercial antibodies including a rabbit polyclonal antibody against an intracellular epitope corresponding to the center region of the Human GRID2 (1:800, 101381-T10, Sino Biologicals); a rabbit polyclonal antibody against an intracellular epitope corresponding to the amino acid residues 852–931 of mouse GluD2 (accession D13266) C-terminal (1:200; AB_2571600, Frontier Institute Japan); and a rabbit polyclonal antibody against an extracellular epitope corresponding to the amino acid residues 206–218 of rat GluD2 (accession Q63226) (1:200, AGC-039, Alomone). All incubations were done overnight at 4°C. Serum samples from 2 reported patients² with GluD2 antibodies (provided by Dr. S Irani) were used as positive human controls. Secondary antibodies included biotinylated goat anti-human immunoglobulin G (IgG) (1:2000; BA-3000, Vector Laboratories) or biotinylated goat anti-rabbit IgG (1:1,000; BA-1000, Vector Laboratories) incubated for 1 hour at room temperature (RT). Reactivity was developed with a standard avidin-biotin immunoperoxidase technique.

Cell-Based Assay

HEK293T cells were transfected with 2 different plasmids, as reported,⁶ including (1) a commercially available plasmid containing the human GluD2 clone with a Myc tag at the C-terminal (accession number: NM_001510, Asp24-Ile1007; catalog number RC214449; Origene) and (2) a custom made plasmid with the human GluD2 (NM_001510) subcloned into the pHLsec vector (PMID: 17001101) immediately downstream of the secretion signal sequence and an external hemagglutinin peptide (YPYDVPDYA) (cloning procedures performed by GenScript). Transfected live cells were incubated with patient or control serum (1:50) for 1 hour at 4°C, washed with phosphate-buffered saline, and fixed with 4% paraformaldehyde for 10 minutes. Cells were then incubated with a secondary antibody goat anti-human IgG Alexa Fluor 594 (1:1,000; A11014, Invitrogen) (classical 2-step method) or alternatively with an unlabeled secondary goat anti-human Fc-specific antibody (1:750; A31125, Fisher) for 1 hour at RT, followed by a tertiary donkey anti-goat IgG Alexa Fluor 568 (1:750, Invitrogen, A11057) (3-step method), as reported.² Coverslips were mounted with PrologGold with DAPI (P36935, Invitrogen) and results were captured with a fluorescence microscope (Zeiss Axioimager M2) using Axiovision software (Zeiss, Oberkochen, Germany).

The expression of the plasmids in CBA was confirmed with the 3 indicated commercial antibodies (diluted 1:1,000) after

Table 1 General Features of Adult and Pediatric Patients With Opsoclonus-Myoclonus Syndrome

	Pediatric patients	Adult patients
Number of patients	45	158
Median age, y (IQR)	2 (1–6)	43 (31–59)
Female (%)	21/45 (47)	86/158 (54)
Tumor associated (%)	10/45 (22) ^a	53/158 (34) ^b
No tumor (%)	35/45 (78)	105/158 (66)
Cell surface antibodies	3 unknown	15 (8 GlyR, 2 NMDAR, 1 GABAbR, 1 AMPAR, 3 neuronal surface unknown) ^d
Intracellular antibodies	3 Hu	16 (8 Ri, 3 Ma2, 2Hu, 1CRMP5, 1Zic, 1GAD65)
GluD2 pattern of brain immunostaining ^c	0/45	0/158
GluD2 CBA-specific reactivity using 2 plasmids and 2 immunofluorescence methods	0/45	0/158

Abbreviations: AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CBA = cell-based assay; CRMP5 = collapsin response mediator protein 5; GABAbR = gamma-aminobutyric acid receptor subunit B; GAD65 = Glutamate decarboxylase 65; GlyR = glycine receptor; GluD2 = glutamate receptor delta 2; IQR = interquartile range; NMDAR = N-methyl-D-aspartate receptor.

^a All neuroblastoma.

^b 11 Small cell lung cancer, 7 non-small cell lung cancer, 9 breast cancer, 6 ovarian teratoma, 5 neuroblastoma, 16 other (2 gastric cancer, 2 lymphoma, 2 ovarian cancer, 2 prostate adenocarcinoma, 1 leukemia, 1 oropharyngeal carcinoma, 1 pancreatic cancer, 1 papillary renal cell carcinoma, 1 testicular seminoma, 1 carcinoma of the thymus, 1 cervical cancer, and 1 unknown primary)

^c Predominant staining of Purkinje cells and molecular layer.

^d Additionally 1 patient with GAD65 antibodies had concurrent IgM HNK1 antibodies, and 2 patients with Ma2 and Zic antibodies had concurrent GlyR antibodies.

cell permeabilization using a previously reported technique.⁶ The corresponding secondary antibody was goat anti-rabbit Alexa Fluor 594 (1:1,000; A11012, Invitrogen), which was used for 1 hour at RT.

Immunoabsorption Studies

Randomly selected representative sera with equivocal reactivity in the 3-step CBA were immunoabsorbed with HEK293T cells expressing GluD2 or nontransfected cells, as reported.⁷

Standard Protocol Approvals, Registrations, and Patient Consents

The study received approval from the local ethics committees of the Hospital Clinic-IDIBAPS University of Barcelona and University of Pennsylvania. Patients or proxies gave written informed consent for the storage and use of serum and CSF samples and clinical information for research purposes.

Data Availability

All data are reported within the article and available anonymized by request from qualified investigators.

Role of the Funding Source

The funders of the study had no role in the design, data collection, data analyses, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit the study for publication.

Results

All patients had typical features of OMS, which in 22% of pediatric cases were associated with neuroblastoma and in 34% of adults with different types of cancers (see tumor types in table 1). Serum samples were assessed by rat brain immunohistochemistry, which showed the patterns of tissue reactivity corresponding to the antibodies listed in table 1. No other distinct patterns of reactivity were identified; specifically, we did not find any consistent or predominant pattern of reactivity of patients' serum with Purkinje cells, molecular layer, granular cell layer, or deep cerebellar nuclei of cerebellum of rat. In contrast, the 3 indicated commercial antibodies used for brain immunostaining showed intense reactivity with Purkinje cells and the molecular layer of cerebellum (where GluD2 is highly enriched^{3,4}) and to a much lesser degree with other brain regions. Compared with this reactivity, the sera of the 2 patients with GluD2-ab (used here as controls)² showed substantially milder staining of the molecular layer of cerebellum and Purkinje cells (figure 1).

Although the expression of both GluD2 plasmids was confirmed with the 3 indicated commercial antibodies, none of the patients with OMS or controls had GluD2-ab using CBA and the standard 2-step immunofluorescence method (figure 1). The 3-step method (as reported in reference 2) was also negative in all cases but showed more frequent equivocal reactivity (table 2). This (usually mild) reactivity occurred independently of the plasmid used; some serum samples showed nonspecific reactivity with one of the plasmids and other sera with the other plasmid.

(A–C) Reactivity of a commercial glutamate receptor delta 2 antibody (GluD2-ab) (AB_2571600, frontier institute Japan) with a sagittal section of rat brain (A) showing the main regions where GluD2 is expressed: molecular layer of cerebellum and Purkinje cells (B). The antibody also reacts with a 3-step CBA expressing GluD2 (C, antibody binding shown in red). Similar studies were performed with another commercial antibody (101381-T10, Sino Biological) (D–F), a human serum with GluD2-ab (G–I), a representative patient with opsoclonus-myoclonus syndrome (OMS) of our study (J–L), and a representative healthy blood donor (M–O). Note the intense reactivity of the 2 commercial antibodies with GluD2-enriched regions (molecular layer and Purkinje cell layer). The serum of a patient with GluD2-ab (used here as a positive human serum sample) showed milder reactivity with these cerebellar regions and the CBA. (A) Representative sample of the 203 patients with OMS is negative by tissue staining and CBA. Scale bars: M = 2000 μ m; N = 200 μ m; O = 20 μ m.

Immunoabsorption of the samples with HEK293T cells expressing GluD2 did not abrogate the equivocal staining, indicating that it was not antigen-specific (figure 2).

Overall, the consistent lack of reactivity of serum of patients with OMS or neuroblastoma with Purkinje cells and the molecular layer of cerebellum (where GluD2 is intensively expressed^{3,4}) and the lack of specific reactivity with CBA using 2 different GluD2 plasmids suggest that GluD2-ab are not biomarkers of OMS.

Discussion

We did not identify GluD2-ab in 203 patients with OMS. These findings are in contrast with those of a prior report suggesting the presence of GluD2-ab in most children with neuroblastoma-associated OMS.² In that report, the authors emphasized the intense reactivity of patients' antibodies with the granular cell layer and deep cerebellar nuclei of adult rat brain sections. However, this pattern of immunostaining does not correspond to GluD2, which instead is robustly

Table 2 Distribution of Equivocal, Nonspecific, Cell-Based Assay (CBA) Reactivity with Patients' Serum, n (%)

	GluD2, plasmid 1 ^a		GluD2, plasmid 2, ^b 3-step CBA
	2-Step CBA	3-Step CBA	
Pediatric OMS	2/45 (4)	3/45 (7)	3/45 (7)
Adult OMS	7/158 (4)	11/158 (7)	10/158 (6)
Control children	2/90 (2)	4/90 (4)	4/90 (4)
Control adults	4/82 (5)	6/82 (7)	7/82 (8.5)

Abbreviations: GluD2 = glutamate receptor delta 2; OMS = opsoclonus-myoclonus syndrome.

^a Plasmid 1 = GluD2 clone with a Myc tag at the C-terminal (accession number: NM_001510, Asp24-Ile1007; catalog number RC214449; Origene).

^b Plasmid 2 = custom made plasmid with the human GluD2 (NM_001510) subcloned into the pHSec vector (PMID: 17001101) immediately downstream of the secretion signal sequence and an external hemagglutinin peptide (YPYDVPDYA).

expressed in the molecular cell layer of cerebellum and Purkinje cells.^{3,4}

Considering the distinctive pattern of GluD2 expression in cerebellum (Purkinje cells and mainly molecular layer), it is unlikely that the presence of GluD2-ab were missed in our previous study where 114 adult patients with OMS were extensively investigated for autoantibodies.¹ However, the possibility that only a subset of adult patients could have GluD2-ab or that these antibodies may only occur in children with OMS led us to re-examine here all available serum samples we previously reported (103/114)^{1,8} and added 55 adults and 45 pediatric patients with OMS identified since those reports. To determine whether technical or methodologic changes could explain our different results, we compared live CBA using a conventional, direct, 2-step immunofluorescence method with that used by Berridge et al.,² in which an extra step (tertiary fluorescent antibody) was introduced. We found that the extra step was unnecessary and in some cases added nonspecific staining (background).

The current findings with tissue immunostaining and CBA, and the well-defined distribution of GluD2 in Purkinje cells and

molecular cell layer of cerebellum,^{3,4} have several practical implications. First, they do not support that the pattern of immunostaining (predominant in granular cell layer and deep cerebellar nuclei) identified in some patients with OMS correspond to GluD2 antibodies, suggesting that other antibodies (yet unknown) may be present in some patients.² Second, we did not identify a consistent pattern of reactivity with the granular cell layer or deep cerebellar nuclei in our cohort of adult and pediatric patients with OMS. Third, we did not find GluD2-ab either, overall suggesting that these antibodies cannot be considered biomarkers of OMS. Finally, OMS is easily identified on direct clinical examination (it does not require clinical criteria or biomarkers for the diagnosis), however, a better knowledge of the underlying mechanisms involved could potentially be used to separate nonparaneoplastic from paraneoplastic cases, and perhaps refine the treatment approach according to different pathogenic mechanisms. The underlying mechanisms of most adult and pediatric cases of OMS are unknown and still waiting to be elucidated.

Acknowledgment

The authors thank Eva Caballero and Esther Aguilar for technical support in performing the rat brain immunohistochemistry and

Figure 2 Immunoabsorption of Serum of a Patient With Equivocal Reactivity

(A) Equivocal glutamate receptor delta 2 (GluD2) reactivity (using the 3-step technique) of serum from a patient with opsoclonus-myoclonus syndrome. This reactivity is not altered by preabsorption of the serum with HEK293T cells expressing GluD2 (B) or nonexpressing GluD2 (C), indicating that the reactivity is not GluD2-specific. Scale bar = 20 μ m.

cell-based assays and Dr. Sarosh Irani for providing serum samples from patients with GluD2 antibodies.

Study Funding

This study was supported in part by Instituto de Salud Carlos III–Fondo Europeo de Desarrollo Regional (ISCIII-FEDER; PI18/00486 to T.A., PI17/00234 to J.D.); Centro de Investigación Biomédica en Red para Enfermedades Raras (CB15/00010 to J.D.); La Caixa Foundation Health Research Award (LCF/PR/HR17/S2150001 to J.D.); the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)–Generalitat de Catalunya (SGR93 to J.D.); Pla estratègic de recerca i innovació en salut (PERIS), Departament de Salut, Generalitat de Catalunya (SLT006/17/00362 to T.A.); a research grant from Torrons Vicens Foundation to T.A.; a grant from Pablove Foundation (689368 to T.A.); the Hospital Clinic (Resident Award “Josep Font” granted by Hospital Clínic de Barcelona, Research, Innovation and Education Departments to M.G.); Foundation Edmond J Safra, and Fundació CELLEX to J.D.

Disclosure

Dr. Dalmau holds patents for the use of Ma2, NMDAR, GABAbR, GABAaR, DPPX, and IgLON5 as autoantibody tests; receives royalties related to autoantibody tests from Athena Diagnostics and Euroimmun, Inc.; and is editor of *Neurology®: Neuroimmunology & Neuroinflammation*. Dr. Graus receives royalties from Euroimmun for the use of IgLON5 as an autoantibody test and honoraria as Assistant Editor of *MedLink Neurology*. The other authors declare no conflicts of interest related to this manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* April 14, 2020. Accepted in final form October 8, 2020.

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Appendix (continued)

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T. Armangué	Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, Barcelona; CIBERER, Valencia; Sant Joan de Déu Children Hospital, Barcelona, Spain	Collected the clinical data, revised the manuscript for intellectual content
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F. Graus	Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain	Collected the clinical data, revised the manuscript for intellectual content
J. Dalmau	Institut d'Investigacions Biomèdiques August Pi i Sunyer and Hospital Clínic Barcelona; CIBERER, Valencia, Spain; Department of Neurology, University of Pennsylvania, Philadelphia; Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain	Designed and conceptualized the study, interpreted clinical and experimental data, revised manuscript, tables and figures for intellectual content

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Neurology 2021;96:e1082-e1087 Published Online before print December 21, 2020

DOI 10.1212/WNL.0000000000011410

This information is current as of December 21, 2020

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