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Antiglycine receptor antibody related disease: a case series and literature review

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Background and purpose: Antibodies to glycine receptors (GlyR-Abs) were first defined in progressive encephalopathy with rigidity and myoclonus (PERM) but were subsequently identified in other clinical presentations. Our aim was to assess the clinical associations of all patients identified with GlyR-Abs in Queensland, Australia, between April 2014 and May 2017 and to compare these to cases reported in the literature.

Methods: A literature review identified the clinical features of all published GlyR-Ab-positive cases through online databases. A case series was undertaken via collection of clinical information from all patients diagnosed or known to immunology, pathology or neurological services in Queensland during the study period of 3 years.

Results: In all, 187 GlyR-Ab-positive cases were identified in the literature. The majority (47.6%) had PERM, 22.4% had epilepsy, but the remaining 30% included mixed phenotypes consisting of cerebellar ataxia, movement disorders, demyelination and encephalitis/cognitive dysfunction. By contrast, in our series of 14 cases, eight had clinical presentations consistent with seizures and epilepsy and only three cases had classical features of PERM. There was one case each of global fatiguable weakness with sustained clonus, laryngeal dystonia and movement disorder with hemiballismus and tics. The rate of response to immune therapy was similar in all groups.

Conclusion: Antibodies to glycine receptors are linked to a spectrum of neurological disease. The results of the literature review and our case series suggest a greater relationship between GlyR-Abs and epilepsy than previously reported.

Introduction

The spectrum of neurological disease related to autoantibodies targeting central nervous system receptors and regulatory cell surface proteins has been rapidly expanding in the last decade. To date, 16 such target antigens have been identified, characterized by a wide array of clinical syndromes [1]. One such target

recently identified is the post-synaptic glycine receptor (GlyR) which is distributed mainly in the spinal cord, brainstem and cerebellum. GlyR is also found in human hippocampus, but its role is less clear [2]. The GlyR is a glycine-gated chloride ion channel typically expressed on the surface of motor neurons in the brainstem and spinal cord, where it regulates neuronal excitability. Genetic loss of function results in hereditary hyperekplexia.

Antibodies against GlyR (GlyR-Abs) were first reported in a single case study in 2008 [3]. The index patient had a severe presentation of progressive

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encephalomyelitis with rigidity and myoclonus (PERM), which responded slowly but impressively to immunotherapy.

A number of cases of PERM/stiff-person syndrome (SPS) with associated GlyR-Abs were published subsequently [4–12]. The most comprehensive series to date details 52 patients who were identified retrospectively from 779 sera referred to the Oxford Neuroimmunology Service from 2008 to 2012 [13] and included patients from all previous case reports. Seven patients were excluded due to very low GlyR-Abs titres. Thirty-three of the remaining 45 were classified as PERM, and two patients had more typical SPS. Of the remaining patients, four were described as an epileptic encephalopathy, with one case each of recurrent encephalopathy, brainstem encephalitis, acute disseminated encephalomyelitis with optic neuritis, optic neuritis and cognitive decline.

More recently, however, there have been case reports describing GlyR-Abs in patients with epilepsy, responsive to immunotherapy in both adults [14,15] and children [16–18]. In addition, GlyR-Abs have been found in retrospective case series of epilepsy patients screened for the presence of antineuronal antibodies [17–19]. These observations raised questions about the disease associations and clinical relevance of GlyR-Abs.

A retrospective case series of all patients in Queensland, Australia, found to be positive for GlyR-Abs was conducted and our findings were compared with previously reported cases.

Methods

Literature review

The aim of the literature review was to identify all reported cases of neurological disease associated with GlyR-Abs. Cases were identified through a PubMed database search utilizing the search strings 'glycine receptor antibodies' and 'glycine receptor encephalitis'. Additional searches were undertaken to identify articles related to 'glycine', 'PERM', 'stiff-person syndrome' and 'autoimmune epilepsy'. Reference lists of identified papers were searched to find additional papers not captured by the initial search strategy. All identified articles were read in full, with relevant information extracted and summarized.

Case series

A retrospective chart review of all patients identified as having GlyR-Abs in serum and/or cerebrospinal fluid (CSF) was performed. Cases were identified by

contacting neurologists working in southeast Queensland and via case identification through a neuroimmunology laboratory. Patient information was gained through the treating clinicians. Notes, letters, laboratory and electrophysiological results were reviewed as well as neuroimaging and treatment response. All glycine antibody analyses were performed by a quaternary reference laboratory, with 13/14 cases using a cell-based assay of human embryonic kidney cells (HEK293) transfected to express homomeric alpha 1 GlyR subunits [Autoimmune Neurology Diagnostic Laboratory (previously Oxford Neuroimmunology Service), Oxford, UK]. With case 8, an earlier form of the assay was used. Antibody scores (exponential scale from 0 to 4; 0 negative; >1 positive; 4 very strong) were provided on request. Except where indicated, all samples tested negative for all other neuronal cell surface antibodies, including anti-LG1, anti-CASPR2, anti-AMPA and anti-GABA antibodies.

Ethical approval for this study was gained through the Queensland Metro South Human Research and Ethics Committee (HREC/17/QPAH/249). Informed consent was obtained from all patients or next of kin.

Results

Summary of literature review

The literature review identified 187 GlyR-Ab-positive cases. The results are summarized in Table 1. The largest group (47.6% of the total) consisted of patients with PERM/SPS. The second most commonly reported diagnosis was that of epilepsy (22.4% of the total). The remaining 30% were made up of cases of cerebellar ataxia, movement disorders, demyelination and cognitive dysfunction.

The age of onset ranged from 1 to 75 years, with a wide spread in all groups. The mean age of onset appeared lower in the epilepsy group (27.1 years) compared to that of 43.2 years in the PERM/SPS group and 40.7 years in the group encompassing the other neurological presentations. Abnormal magnetic resonance imaging (MRI) and abnormal electroencephalogram (EEG) results were most common in the epilepsy group.

Malignancy was most commonly encountered in the group presenting with PERM/SPS. Tumours were reported for 10 of the 89 PERM/SPS patients, including five thymomas and one case each of marginal B-cell lymphoma, breast cancer, Hodgkin's lymphoma and small-cell lung cancer. Additionally, there were four cases with a past history of malignancy (thymoma and lymphoma, malignant melanoma, breast cancer and thymoma, Hodgkin's lymphoma). There

Table 1 Summary of all published cases divided into clinical groups

	PERM/SPS group	Epileptic seizures group	Other neurological presentation
Number of cases	89	42	56 (24 demyelination/inflammatory, 24 cerebellar ataxia and movement disorders, seven encephalitis, one steroid responsive deafness)
Age of onset range (years)	1–75	1–58	8–70
Mean age of onset (years)	43.18	27.15	40.71
Male:female ratio (not reported)	26:24 (39)	15:22 (5)	5:9 (42)
Number of cases with abnormal MRI brain findings	0 (0%)	10 (24%)	3 (5%)
Number of cases with abnormal EEG findings (number of EEGs reported in parentheses)	1 (frequent sharp waves) (2)	Five cases with epileptiform discharges, four cases with slowing/encephalopathy (9)	0 (0)
Pre-existing other autoimmune conditions	14/89 (16%)	4/42 (10%)	7/56 (13%)
Prior malignancy	4/89 (4%)	0/42 (0%)	0/56 (0%)
Malignancy discovered during acute presentation	10/89 (11%)	0/42 (0%)	7/56 (13%)
No response to immune modulation/died	10/63 (16%)	1/12 (9%)	0/11 (0%)
Partial response to immunotherapy	24/63 (38%)	4/12 (33%)	5/11 (45%)
Substantial/complete response to immunotherapy	29/63 (46%)	7/12 (58%)	6/11 (55%)
Response to immunotherapy not reported/no immunotherapy given	26	30	45

were no cases of malignancy in the group with epilepsy. One study of 112 patients with opsoclonus–myoclonus reported nine cases of GlyR-Abs, of which six were associated with malignancy (four lung cancer, one breast cancer and one testicular seminoma).

In the PERM/SPS group, the results of 63 of 89 cases undergoing immunotherapy were reported; of these, 24 (38%) showed a partial response and 29 (46%) showed a substantial or complete response. In the epilepsy group, only 12/42 patients had information regarding immunotherapy, but the results were similar with four (33%) showing a partial response and seven (58%) a substantial or complete response. In the group representing other neurological presentations, a response to immunotherapy was reported only in 11/56 cases, and the results were again similar, with partial response in five (45%) cases and substantial or complete response in six (54%); nine of these patients presented with demyelination/inflammation syndromes.

Case series results

During the period April 2014 to May 2017, 14 cases of positive GlyR-Abs were identified in Queensland. The individual cases are described in Table 2, with details summarized in Table 3.

The cases were predominantly female with a 11:3 F:M ratio and an age range between 20 and 79 years. Of these, eight patients presented with epilepsy, three patients with PERM/SPS, and the other patients were suffering from hemiballism/tics, laryngeal dystonia

and an atypical neurological syndrome comprising global fatiguable weakness and sustained clonus.

Magnetic resonance imaging brain was normal in six cases with a range of abnormalities found in the others (Table 2). CSF was obtained in nine cases, of which five were normal and four had a high white cell count and/or oligoclonal bands; GlyR-Abs in CSF were tested in three patients, of whom two were negative. A teratoma was detected in one patient, and two others had a past history of cancer.

Immunotherapy was administered in 11/14 patients. In the PERM group, one patient had no response, one patient partial and one patient substantial response to immunotherapy. In the 'Other neurological presentation' group immunotherapy was given to two patients; both had partial or good responses. In the epilepsy group, six patients received immunotherapy, of whom one had no response, one a partial response and four substantial responses (Tables 2 and 3).

Patients benefitting best from immunotherapy in the epilepsy group presented with a clinical syndrome of an acute encephalitis and refractory status epilepticus, often with other associated features. Immunotherapy in those patients usually led to remarkable clinical recovery, even though relapses occurred in some patients (Tables 2 and 3).

Two patients followed a more subacute course, where long-standing (>12 months) epilepsy worsened without an obvious precipitant. Two further cases had no substantial change to their long-standing epilepsy prior to detection of GlyR-Abs (Tables 2 and 3).

Table 2 Summary of GlyR-Abs cases in Queensland over the period from 2014 to 2017

Number	Sex	Age at diagnosis	GlyR-Abs: months after initial assessment – Intensity score (0–4)	Clinical presentation	CSF analysis	MRI brain and EEG results	Tumours newly identified or in past history	mRS (max)	Initial immunotherapy	mRS July 2017	Current immunotherapy	Relapses and response to treatment after GlyR-Abs identification and immunotherapy
1	F	29	4–0 12–2 14–1.5	Status epilepticus, encephalopathy, intubated and ventilated	WCC <1, protein 260, OCB positive	MRI brain: normal study EEG: status epilepticus, subsequent EEGs revealed cortical dysfunction left temporal region	No tumour	5	IVIG, RTX, MMF	0	IVIG for 1 year	Single seizure
2	F	20	50–4	Status epilepticus, intubated and ventilated, headache, diplopia, non-epileptic seizures, behavioural change, myoclonic jerks affecting the upper limbs	WCC <1, protein 340	MRI brain: normal study EEG: status epilepticus, right frontocentral focus	No tumour	5	IVIG, RTX, ketogenic diet	0	RTX	Relapse with status epilepticus. Nil further episodes since rituximab treatment
3	M	57	122–4	PERM with startle, encephalitis, cognitive impairment	WCC <1, protein 497	MRI brain: normal study Normal EEG	No tumour	3	IVIG	1	IVIG	IVIG led to improvement in hand stiffness
4	F	37	1–1.5 8–2.5	Acute encephalitis with seizures, personality change, intubated and ventilated	WCC <1, protein 400	Abnormal MRI with cortical oedema (study performed in context of ICU admission for status epilepticus) EEG: status epilepticus, predominantly left hemispheric	No tumour	5	IVIG, RTX	1	IVIG	No further status epilepticus but seizures continue monthly
5	F	45	1–4 3–CSF 0	Hemiballismus/tic disorder affecting right-side of body	WCC 1, protein 310, OCB positive	MRI brain: two small triangular shaped CSF intense lesions are present within the right cerebellar hemisphere, EEG: normal	Past history of breast cancer 2014 and melanoma 2016	2	St, IVIG	2	IVIG	Improvement in hemiballismus

(Continued)

Table 2 (Continued)

Number	Sex	Age at diagnosis	GlyR-Abs: months after initial assessment – Intensity score (0–4)	Clinical presentation	CSF analysis	MRI brain and EEG results	Tumours newly identified or in past history	mRS (max)	Initial immunotherapy	mRS July 2017	Current immunotherapy	Relapses and response to treatment after GlyR-Abs identification and immunotherapy
6	F	50	2–1.5 6–0	Epilepsy, recurrent status epilepticus, cognitive impairment	CSF: not tested	MRI brain: mild diffuse atrophy VEEG: intermittent slow left temporal and bilateral parietal with sharp waves left occipital region. EEG seizure right parietal region	No tumour	5	IVIg	1	IVIg	Seizures previously weekly, 3 months seizure free on IVIg, currently less severe seizures every 3 weeks
7	F	54	4–2	PERM Cognitive impairment	CSF: protein 270	MRI brain: frontal and temporal lobe atrophy EEG: diffuse slowing	No tumour	5	RTX, St, IVIg	5	Nil	Poor response to immune therapy
8	F	54	60–1.5 60–CSF 0	PERM, propriospinal myoclonus, seizures, limbic encephalitis	CSF: protein 170, WCC 1	Normal MRI brain Normal EEG	No tumour	5	PLEX, AZA, St	2	PLEX, St	Partial response to PLEX
9	M	68	0–4	Seizures, encephalitis, memory disturbance	CSF: not tested	MRI brain: increased T2 signal bilateral temporal lobes Normal EEG	No tumour	5	RTX, St, IVIg	2	St	Good response of epilepsy and encephalitis, ongoing amnesia
10	F	79	0–1.5	Laryngeal dystonia	CSF: not tested	MRI brain: normal EEG: not performed	Prior NSCLC	1	No treatment	1	Nil	
11	F	31	5–1.5 5–CSF 2	Global weakness including respiratory muscles, hyperreflexia, sustained clonus, intubation and ventilation, memory impairment	CSF 44 WCC, 100% monocytes, OCB +ve, protein 400	MRI brain: normal EEG: not performed	Teratoma with neural tissue Also had presence of NMDA receptor antibodies in serum and CSF and VGKC antibodies in serum	5	St, IVIg, BSO with removal of teratoma	0	Nil	Excellent response with complete remission of symptoms

(Continued)

Table 2 (Continued)

Number	Sex	Age at diagnosis	GlyR-Abs: months after initial assessment – Intensity score (0–4)	Clinical presentation	CSF analysis	MRI brain and EEG results	Tumours newly identified or in past history	mRS (max)	Initial immunotherapy	mRS July 2017	Current immunotherapy	Relapses and response to treatment after GlyR-Abs identification and immunotherapy
12	M	37	10–0 12–1.5	Epilepsy, progressive course over 18 months with little response to antiepileptic medication	CSF: 15 WCC, protein normal	MRI brain: small area of cortical dysplasia VEEG: 2 clinical seizures comprising bilateral hand automatisms (left > right), expression of disgust, oral automatism, left arm semi-dystonic posturing	No tumour	2	St, IVIG	2	IVIg	Limited/no response to immunotherapy
13	F	39	120–3	History of epilepsy since adolescence with seizure frequency worsening over the last 2–3 years	CSF: not tested	MRI brain: hemispheric atrophy EEG: intermittent slow regional right and left temporal, sharp waves right anterior temporal, EEG seizure left parietal region	No tumour	1	Anticonvulsant therapy, no immunotherapy	1	Nil	
14	F	24	240–4	Long-standing history of epilepsy	CSF: not tested	MRI brain: normal study EEG: left frontotemporal spikes	No tumour	1	Anticonvulsant therapy, no immunotherapy	1	Nil	

AZA, azathioprine; BSO, bilateral salpingo-oophorectomy; CSF, cerebrospinal fluid; EEG, electroencephalogram; F, female; GlyR-Abs, antibodies to glycine receptors; ICU, intensive care unit; IVIG, intravenous immunoglobulins; M, male; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NMDA, *N*-methyl-D-aspartate; NSCLC, non-small-cell lung cancer; OCB, oligoclonal bands; PERM, progressive encephalomyelitis with rigidity and myoclonus; PLEX, plasma exchange; RTX, rituximab; St, steroid therapy; VEEG, video electroencephalogram; VGKC, voltage gated potassium channel; WCC, white cell count. GlyR-Ab levels given as an exponential scale from 0 to 4; 0 negative; >1 positive; >4 very strong.

Table 3 Summary of clinical characteristics of the Queensland case series

	PERM/SPS group	Epileptic seizures group	Other neurological presentations
Number of cases	3	8	3
Age of onset range (years)	55–60	20–68	31–79
Mean age of onset (years)	57.33	38.00	51.66
Male:female ratio	1:2	2:6	0:3
Number of cases with abnormal MRI findings	1	5	1
Number of cases with abnormal EEG findings (EEGs performed)	1 (1)	7 (8)	0 (0)
Pre-existing other autoimmune diseases	0	0	1
History of prior malignancy	0	0	2
Malignancy discovered during acute presentation	0	0	1
No response to immune modulation/died	1	1	0
Partial response to immunotherapy	1	1	1
Substantial/complete response to immunotherapy	1	4	1
Response to immunotherapy not reported/no immunotherapy given	0	2	1

Discussion

The third largest cohort of patients with GlyR-Ab-associated neurological disease in the literature is reported and the largest series from a defined geographical area and time interval. Eight of 14 of our patients were suffering with epilepsy, three with a presentation consistent with PERM and SPS and three with a variety of other neurological syndromes. Response to therapy, where undertaken, was in general favourable with partial or full resolution of symptoms in nine of 11 treated patients. Of particular interest is the subgroup of GlyR-Ab-positive epilepsy patients refractory to anticonvulsant therapy, who responded well to immunotherapy. Limitations of our data include the retrospective nature of the presented cases and incomplete characterization of the antibodies with regard to titration and CSF antibody status.

In comparison, a comprehensive review of all reported cases of GlyR-Abs to date revealed 47.6% of cases diagnosed with SPS/PERM, 22.4% of patients suffering from epilepsy with the remaining 30% of patients being diagnosed with a wide variety of different syndromes.

Our results are therefore somewhat discrepant with the previous literature, with a higher number of patients suffering from epilepsy [13,19]. This could partially be explained by the different methodologies used for case ascertainment in the two studies. The patients previously studied were collated from a quaternary referral laboratory; as GlyR-Abs were at that stage thought to be strongly associated with PERM, it is likely that patients referred for testing over the first years of availability were preselected for that diagnosis. Epilepsy and encephalopathy, however, were also reported to be part of the initial syndrome in 36% of

cases in the Carvajal-González paper [12]. Subsequently, other phenotypes were identified in individual patients with seizures [14–18] and in epilepsy populations [20,21].

This variability of clinical syndromes may be explained by focal breakdown of the blood–brain barrier, allowing entry of peripherally produced antibodies into limited anatomical areas of the central nervous system (CNS). Alternatively, it could be explained by antibody specificity to the different GlyR subtypes. Possibly, GlyR-Abs could be an epiphenomenon of immunotherapy responsive CNS inflammation associated with a proepileptic state.

The GlyR is an inhibitory receptor, consisting of α and β subunits, of which the α -subunit has four different isoforms giving rise to four different GlyRs in human adult CNS [22]. GlyR α 1 is the best characterized glycine receptor and was the predominant antigenic target [12]; dysfunction of the GlyR α 1 in brainstem and spinal cord, by mutation, toxic agents (e.g. strychnine) or immune mediated, leads to hyperkplexia in humans [3,23,24]. GlyR α 2, 3 and 4 are found to be more widespread in mammalian CNS, including hippocampus, striatum, cerebellum and cortex [13,25,26]. Cross-reaction between Gly α 1 Abs and the other alpha subunits has been seen in 50% of previously reported cases [13]. Neuronal hyperexcitability mediated by toxic antibody-mediated inhibition of GlyRs by strychnine or tranexamic acid has been linked to seizures in animal models and historically in humans [27,28]. Although the role of GlyRs in controlling seizures is not clear, GlyR agonists have been shown to have an antiepileptic effect in rat models [29], and *in vitro* tonic inhibition of high affinity hippocampal GlyRs leads to epileptiform activity [30]. Thus, antibody-mediated loss of GlyRs (as shown

in vitro [12]) at various sites in the CNS could potentially be a cause of epilepsy.

Conclusion

Although the neuronal surface antibodies that have been identified to date are described in association with specific clinical syndromes, it is becoming clear that in clinical practice the associations are not always syndrome-specific. It appears that, in addition to the well-established connection of GlyR-Abs to SPS and PERM, a subset of patients with refractory epilepsy have detectable GlyR-Abs and can respond to immune therapy.

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Disclosure of conflict of interest

The University of Oxford holds patents and receives royalties for MuSK, CASPR2 and LGI1 antibodies. AV, SRI and PW receive a proportion of the royalties.

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