Original Article

Clinical Profile and Treatment Response in Patients with CASPR2 Antibody-Associated Neurological Disease

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Abstract

Background: The clinical spectrum of contactin-associated protein-like 2 (CASPR2) antibody-associated disease is wide and includes Morvan syndrome. Studies describing treatment and long-term outcome are limited. **Aims:** We report the clinical profile and emphasize response to treatment and long-term outcome in eight patients with CASPR2-antibody-associated disease. **Methods:** Clinical, radiological, electrophysiological, treatment, follow-up, and outcome data were collected by retrospective chart review. **Results:** Clinical manifestations included Morvan syndrome (n = 7) and limbic encephalitis (n = 1). None of the patients were positive for LGI1 antibody. Associated features included myasthenia (n = 1), thymoma (n = 1), and dermatological manifestations (n = 4). Patients were treated with intravenous methylprednisolone and plasma exchange during the acute symptomatic phase followed by pulsed intravenous methyl prednisolone to maintain remission. Mean-modified Rankin score at admission (pre-treatment), discharge, and last follow-up were 3.75, 2.5, and 0.42, respectively. One patient with underlying thymoma and myasthenic crisis died. The other seven patients were followed up for a mean duration of 19.71 months. All of them improved completely. Relapse occurred in one patient after 13 months but responded favorably to steroids. **Conclusion:** CASPR2 antibody-associated disease has favorable response to immunotherapy with complete improvement and good outcome. Underlying malignancy may be a marker for poor prognosis.

Keywords: Autoimmune encephalitis, contactin-associated protein-like 2 (CASPR2), Morvan syndrome, paraneoplastic neurological disease, voltage-gated potassium channel

Introduction

A number of autoimmune neurological diseases associated with antibodies against cell surface or intracellular antigens have been described over the past few decades. This includes disorders associated with antibodies to contactin-associated protein-like 2 (CASPR2), a voltage-gated potassium channel-associated transmembrane protein which belongs to the neurexin superfamily of cell adhesion proteins. CASPR2 plays a key role in the formation and regulation of synapses and is expressed in both the central nervous system (CNS) and peripheral nervous system (PNS).[1] CASPR2 antibody-associated disease can affect both CNS and PNS. The classical syndrome associated with this antibody is eponymous with Augustin Morvan, who first described this entity.[2] Morvan syndrome is characterized by peripheral nerve hyperexcitability, dysautonomia, insomnia, and fluctuating encephalopathy.[3] In addition to Morvan syndrome, limbic encephalitis, cerebellar ataxia, cognitive disturbance, and rarely movement disorders have been recognized as the presenting features of CASPR2 associated neurological disorder.[4-9] Other uncommon manifestations include Guillain–Barre-like syndrome,[10,11] chronic pain,[12] Creutzfeld–Jakob disease-like illness,[13] and amyotrophic lateral sclerosis with frontotemporal dementia-like syndrome.[14] CASPR2 antibody-associated disease may occur concurrently with other autoimmune disorders (most common being myasthenia gravis) as well as in the setting of neoplasms (most common being thymoma).[15] Immunosuppression is the mainstay of treatment. A few studies have reported response to steroids, plasma exchange, and intravenous immunoglobulin (IVIg). Steroid-sparing agents including azathioprine, mycophenolate, cyclosporine, cyclophosphamide, and rituximab have been used in refractory cases.[15-17]

Thus, there is some literature describing the phenotypic spectrum of CASPR2 antibody-associated neurological diseases particularly Morvan syndrome. But CASPR antibody-associated neurological disorder is relatively uncommon among the

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autoimmune encephalitis syndromes and the available literature mostly comprises case reports. Cohort studies have included a heterogenous population with dual positivity for CASPR and Leucine-rich glioma-inactivated protein 1 (LGI1) antibodies. Literature focusing on the treatment protocols, response, and outcome in CASPR antibody-associated neurological disorder is further limited,[16,17] and there are no studies from India. In this study, we describe the clinical course in patients with CASPR2 antibody-associated disease with emphasis on treatment and outcome.

Patients and Methods

This study is a retrospective chart review carried out at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, which is a tertiary-care teaching hospital in South India. Between 2014 and 2020, 1475 patients were seen in a single neurology unit for clinically suspected autoimmune encephalitis. These patients underwent testing for panel of autoantibodies including CASPR2, LGI1, *N*-methyl-d-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)1, AMPA2, and gamma-aminobutyric acid (GABA) antibodies using the commercially available cell-based assay (Euroimmun®) in the serum and/or cerebrospinal fluid (CSF). Among these, 238 tested positive for one or more of the autoantibodies and 16 patients tested positive for CASPR2 antibody. Of the 16 patients, 8 patients who were investigated for encephalopathy ($n = 7$) and refractory seizures ($n = 1$) did not complete evaluation and refused treatment. Since their data were inadequate and no follow-up was available, these eight patients were excluded from the study. The medical records of the remaining eight patients were reviewed. Details regarding clinicodemographic profile, neuroimaging observations, CSF, electroencephalography, electroneuromyography, autonomic function testing, polysomnography, and other laboratory investigations were noted. The following tests were carried out for identifying underlying malignancy: (i) paraneoplastic antibody panel, (ii) computed tomogram (CT) of chest and abdomen, and (iii) positron emission tomography (PET) CT or magnetic resonance imaging (MRI) of the whole body.

All patients received pulsed intravenous methyl prednisolone for inducing and maintaining remission. Plasmapheresis was given in case of severe manifestations. The duration of hospital stay as well as outcome at discharge and last follow-up were collected. The modified Rankin score (mRS) was used to assess the disability before treatment, at discharge, and at last follow-up. The data were entered in a predesigned proforma and incorporated into a Microsoft Excel spreadsheet for analysis. Continuous variables were expressed as mean ± standard deviation while categorical data were expressed in percentages.

Results

The clinicodemographic features and laboratory findings of the patients are summarized in Tables 1–3, Figure 1a–g, and Supplementary Video. Antecedent events included surgery for hydrocele in patient 4 and intake of Ayurvedic medications in patient 5. Abnormal brain MRI was noted in two patients: (i) patient 6 had features of posterior reversible encephalopathy syndrome, probably due to autonomic dysfunction; and (ii) patient 8 had T2 and FLAIR hyperintensities in bilateral thalami, posterior limb of internal capsule, brainstem, and cerebellar hemispheres [Figure 1e–g]. Investigations for

Table 1: Clinicodemographic features and laboratory findings in patients with CASPR2 antibody-associated disease in the present cohort

Clinical characteristics	Observed values
Male:female	5:3
Mean age (years)	35.75 (SD 16.38) (range, 12-54 years)
Mean duration of illness (months)	2.5 (SD 1.41) (range, 1-5 months)
Central nervous system manifestations	
Encephalopathy	3/8
Cognitive impairment	2/8
Psychiatric manifestations	4/8
Insomnia	7/8
Seizures	1/8
Hemiparesis	2/8
Tremor	2/8
Peripheral nervous system manifestations	
Pain	6/8
Paraesthesia	3/8
Peripheral nerve hyperexcitability	6/8
Autonomic dysfunction	
Cardiovascular	6/8
Gastrointestinal	3/8
Genitourinary	3/8
Sweating abnormalities	3/8
Systemic manifestations	
Fever	2/8
Dermatological	3/8
Loss of appetite/weight	3/8
Hydrocele	1/5
Other autoimmune disorders	2/8
Associated tumor	1/8
Abnormal MRI of brain	2/7*
Abnormal PET of whole body (CT/MRI)	0/3
Anti-CASPR2 antibody positivity in serum	8/8
Anti-CASPR2 antibody positivity in CSF	1/4*
Hyponatremia	3/8
Abnormal EEG	0/5*
Abnormal NCS	1/7*
Neuromyotonia on needle EMG	4/4*
Abnormal PSG	1/1*
Abnormal ECG	7/8

CSF: Cerebrospinal fluid; CT: computed tomogram; ECG: electrocardiogram; EEG: electroencephalogram; EMG: electromyogram; MRI: magnetic resonance imaging; NCS: nerve conduction study; PET: positron emission tomogram; PSG: polysomnogram; SD: standard deviation. *Denominator indicates the number of patients in whom the information was available

Table 2: Clinical features of individual patients with CASPR2 associated disease in the present study

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Duration of illness (months)	2	5	3	1	2	1	2	4
Encephalopathy	N	N	N	N	N	Y	Y	Y
Cognitive impairment	N	Y	Y	N	N	NA	NA	NA
Seizures	N	N	N	N	N	N	N	Y
Psychiatric manifestations	Y	Y	N	N	N	N	Y	Y
Insomnia	Y	Y	Y	Y	Y	Y	Y	N
Pain	Y	Y	Y	Y	Y	Y	NA	N
Parasthesias	Y	N	Y	N	N	Y	NA	N
Peripheral nerve hyperexcitability	Y	Y	Y	Y	Y	N	Y	N
Autonomic dysfunction								
Cardiovascular	Y	N	Y	N	Y	Y	Y	Y
Gastrointestinal	N	Y	N	N	Y	N	Y	N
Sweating abnormalities	N	N	Y	N	Y	N	Y	N
Genitourinary	Y	Y	N	N	Y	N	N	N
Fever	N	N	N	N	N	N	Y	Y
Dermatologic manifestations	N	Y (exfoliation in palms, dermatitis herpetiformis)	N	Y (pruritus)	Y (transient macular rashes)	N	N	Y (exfoliation in palms)
Loss of weight and/or appetite	N	N	Y	Y	N	Y	N	N
Other autoimmune diseases	N	N	N	N	Y (vitiligo)	N	Y (MG)	N
Tumor	N	N	N	N	N	N	Y (thymoma)	N
Other features	N	N	Postural tremor	N	N	Transient hemiparesis	N	Hemiparesis, tremor, diplopia

MG: Myasthenia gravis; N: no; NA: information not available; Y: yes

Table 3: Laboratory findings of individual patients with CASPR2 antibody-associated disease in the present study

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Abnormal neuroimaging	N	N	N	N	N	Y (PRES)	N	Y (thalamus, internal capsule, brainstem, cerebellar)
Abnormal EEG	N	N	ND	N	ND	N	ND	N
Abnormal ENMG	Y (NMT)	Y (NMT)	N	Y (NMT)	Y (NMT)	Y (sensorimotor axonal neuropathy)	ND	N
Abnormal ECG	Y (tachycardia)	Y (tachycardia)	Y (tachycardia, U waves)	N	Y (tachycardia)	Y (tachycardia)	Y (tachycardia, ventricular ectopics)	Y (tachycardia)
Cardiac autonomic dysfunction (AFT)	Y	Y	Y	Y	Y	ND	ND	ND
Abnormal PSG	Y (absent sleep stages)	ND	ND	ND	ND	ND	ND	ND
CSF pleocytosis	N	N	N	N	N	Y	ND	Y
Hyponatremia	N	Y	N	N	Y	Y	N	N
Other autoantibodies	N	N	N	N	N	N	Y (AchR antibody)	N
Abnormal CT chest and abdomen	N	N	N	N	ND	N	Y (thymoma)	N
Abnormal PET CT/MRI	ND	N	ND	ND	N	ND	ND	N

AchR: Acetylcholine receptor; AFT: autonomic function test; CSF: cerebrospinal fluid; CT: computed tomogram; ECG: electrocardiogram; EEG: electroencephalogram; ENMG: electroneuromyogram; MRI: magnetic resonance imaging; N: no; ND: not done; NMT: neuromyotonia; PET: positron emission tomography; PRES: posterior reversible encephalopathy syndrome; PSG: polysomnogram; Y: yes

systemic malignancy revealed thymoma in patient 7. Of the four patients who underwent CASPR2 antibody testing in CSF, only one was positive (patient 8).

Treatment and Outcome

The mean interval between the onset of symptoms and initiation

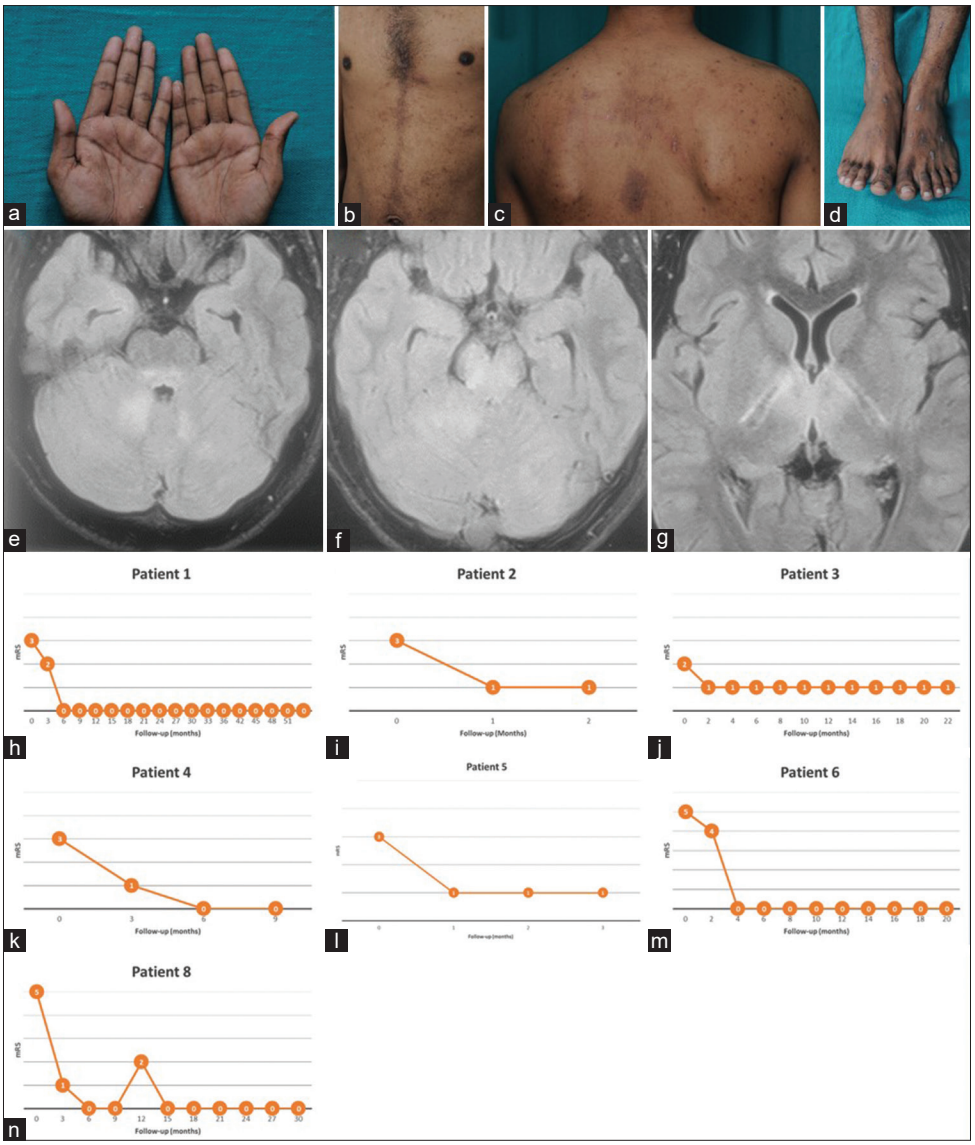

Figure 1: (a–d) Skin changes in patient 2 in the form of palmar exfoliation (a), macular rashes over anterior (b) and posterior (c) aspect of trunk and scaly hyperkeratotic macular rashes over dorsum of feet (d). (e–g) Axial FLAIR sections of brain MRI of patient 8 show hyperintensity in brainstem, cerebellar hemispheres, bilateral thalami, and posterior limbs of internal capsule. (h–n) Serial change in modified Rankin score in individual patients included in the present study

of treatment was 2.75 ± 1.39 months (range, 1–5 months). The details of treatment and outcome are summarized in Table 4 and Figure 1h–n. All patients were treated with intravenous pulsed methylprednisolone (30 mg/kg/day up to a maximum of 1 g/day), which was administered over 4–5 h every day for 5 days to induce remission in the acute phase. Plasma exchange (200 ml/kg of plasma exchanged in 3–7 sessions on alternate days) was given in seven patients in the acute phase if response to methyl prednisolone was poor or patients had severe manifestations (mRS of 3 or more). The treatment algorithm is presented in Figure 2. Patient 7 also required intensive care and mechanical ventilation in view of concurrent myasthenic crisis. This patient died due to myasthenic crisis and nosocomial infection after 11 weeks of hospital stay. This patient has been reported earlier.[18] Except for patient 7, rest of the patients improved in all symptoms at the time of hospital discharge (mean duration of hospital stay: 29.625 ± 25.73 days, range: 8–90 days).

Subsequently, these patients were administered monthly pulsed intravenous methylprednisolone in order to maintain remission. They were reviewed clinically once in 3–6 months in the outpatient department. Serum CASPR antibody was tested once in 6–12 months in order to ascertain sustained serological remission. The mean duration of follow-up after discharge was 19.71 ± 17.61 months (range, 2–52 months). Four patients were followed up for longer than 1 year. Patient 1 was advised to discontinue steroids after 36 months in view of sustained clinical and serological remission and there was no relapse during follow-up of 16 months after stopping treatment. Patient 6 discontinued treatment after 2 months on her own, but there was no clinical or serological relapse during subsequent

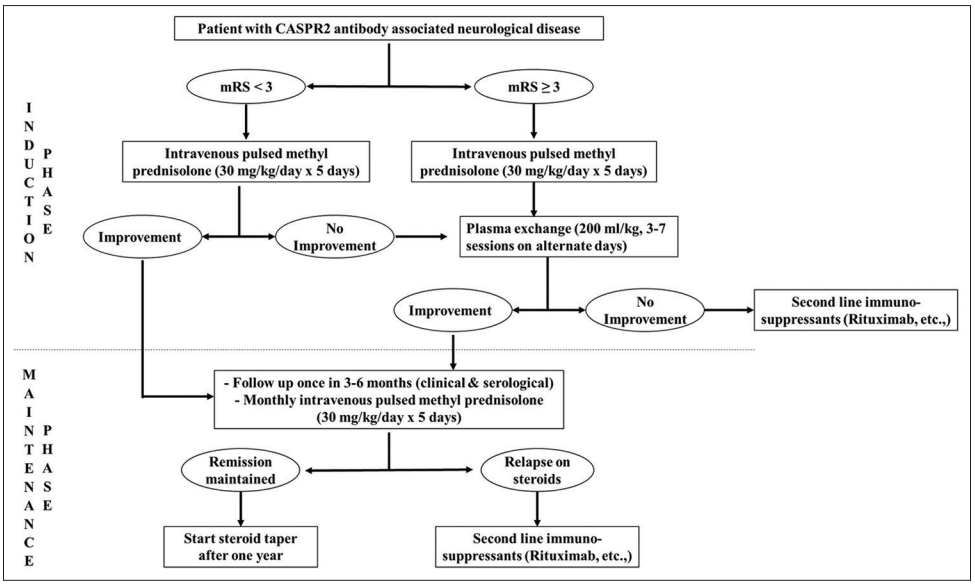

Figure 2: Treatment algorithm for patients with CASPR2 antibody-associated neurological disease

Table 4: Treatment details and outcome of individual patients with CASPR2 antibody-associated disease in the present study

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Duration between onset of symptoms and initiation of treatment (in months)	3	5	3	1	2	1	3	4
Steroids	Y	Y	Y	Y	Y	Y	Y	Y
Plasma exchange	Y	Y	Y	N	Y	Y	Y	Y
Medication for neuropathic pain	Y	Y	Y	Y	Y	Y	N	N
Others	NA	NA	NA	NA	NA	NA	ICU care, ventilation	AED
Duration of hospital stay (days)	23	18	16	8	22	23	90	37
Duration of follow-up (months)	52	2	22	9	6	20	*	30
mRS at admission	3	3	3	3	3	5	5	5
mRS at discharge	2	1	1	1	1	4	6	4
mRS at last follow-up	0	1	1	0	1	0	NA	0
Improvement at last follow-up/discharge	Y	Y	Y	Y	Y	Y	N (died)	Y
Repeat CASPR2 antibody at latest follow-up	Negative	NA	Negative	NA	Negative	Negative	NA	Weakly positive
Relapse	N	N	N	N	NA	N	Not applicable	Y

AED: Antiepileptic drugs; ICU: intensive care unit; N: no; NA: information not available; Y: yes; mRS, modified Rankin score. *Patient died

follow-up of 20 months. Patient 3 was advised to taper steroids after 1 year, and there was no relapse during subsequent 10 months of follow-up. Patient 8 had presented with seizures, behavioral disturbances, and encephalopathy of 5 months duration and treated with steroids and plasma exchange in the acute phase followed by monthly pulse steroids. She improved completely and the maintenance dose of steroids had been reduced after 12 months of treatment. She had a relapse 1 month after reduction in steroid dose. Clinical features during relapse included dystonia of jaw and left upper limb and behavioral disturbance in form of irritability and anger outbursts. After reinitiating steroids and plasma exchange, patient improved gradually over 2 months.

Symptomatic treatment included medications for neuropathic pain which was given in 6 patients and these included phenytoin ($n = 4$), carbamazepine ($n = 1$), gabapentin ($n = 2$), pregabalin ($n = 2$), amitriptyline ($n = 1$), duloxetine ($n = 1$), and baclofen ($n = 1$). Multiple (>2) medications were required for pain control in four patients. In all patients, it was possible to discontinue medications for neuropathic pain during follow-up. Patient 8 required antiepileptic drugs for seizures.

Discussion

CASPR2 antibody-associated diseases are rare but potentially treatable neurological disorders with broad clinical spectrum.[4] In this study, we investigated the clinical spectrum of CASPR2 antibody-associated disease with particular emphasis on response to immunotherapy and outcome. Salient observations regarding the clinical profile include the following:

1. There was male preponderance in our study similar to that noted in other studies.[3,15-17,19,20] The male reproductive system, especially the prostate, might harbor antigens that trigger autoimmunity.[21] Antecedent events including surgery for hydrocele and use of alternative medication were noted in two patients. Both events have been previously reported in association with Morvan syndrome.[16,22,23]
2. In the present study, all except one patient had features of Morvan syndrome with involvement of both CNS and PNS. Seizures, cerebellar involvement, and movement disorders were uncommon in our cohort, but they have been highlighted in previous studies.[3,15-17,19,20]
3. We noted systemic features in the form of skin lesions while other autoimmune diseases and malignancies were occasionally seen. Association with other autoimmune diseases and malignancy is well known but skin manifestations have not been described in previous studies.[3,4,15,16]
4. Similar to other studies, neuroimaging was normal in most of our patients.[15-17,19] None of our patients had concomitant LGI1 antibody positivity and CASPR2 antibody was detected in CSF in one out of the four patients who were tested. It is unclear whether the site of antibody synthesis is systemic or intrathecal as CASPR2 antibodies can be detected in either serum or CSF.[24,25] Patient 8 in the present study who had CSF CASPR2 antibody positivity presented with the phenotype of limbic encephalitis. This observation has been reported in another study and is in contrast to patients without CSF antibody who have features of Morvan syndrome.[25]

We administered steroids since they are the first line of management in other systemic and neurological immune-mediated disorders.[26] Pulsed intravenous methyl prednisolone was chosen in view of our prior experience of its effectiveness, safety, and tolerability in patients with anti-NMDA receptor encephalitis.[27] Other second-line immunosuppressants like rituximab were reserved for patients who had insufficient response to an adequate trial of steroids or relapsed. There are no standard recommendations or established consensus practice guidelines regarding the dosage and duration of treatment since CASPR-associated neurological disorder is an uncommon entity among the autoimmune encephalitis syndromes. Available literature regarding the use of and response to immunosuppressants is sparse, with most studies being single-case reports and a few cohort studies. The duration of follow-up in these studies ranged from 3 months to 4 years. Various immunotherapies have been tried including steroids (oral and intravenous),

Table 5: Summary of previous studies reporting treatment details and outcome in patients with CASPR2 antibody-associated disease

Author (years)	Number of patients	Treatment	Median follow-up (months)	Outcome
Ligouri *et al*., 2001	1	Plasma exchange	26	Died
Irani *et al*., 2010	19	Not available	Not available	Improvement in 68% Death in 21% (all had underlying tumors)
Irani *et al*., 2012	29* (6 CASPR2 positive, 3 LGI1 positive, 15 dual positive, 2 no testing)	Steroids, IVIg, plasma exchange, azathioprine, cyclosporine, cyclophosphamide	Not available	Improvement in 62% Death in 31% (two-third had underlying tumor) Relapse in 6.8%
Tuzun *et al*., 2013	1	IVIg	Not available	Died (had underlying lung adenocarcinoma)
Fabbri *et al*., 2014	1	Steroids	Not available	Partial improvement
Rosch *et al*., 2014	2	IVIg	4.5 (range, 3-6)	Improvement in both
Sunwoo *et al*., 2015	5	Steroids, IVIg, mycophenolate	8 (range, 3-18)	Improvement in 80%
Bien *et al*., 2016	22	Steroids	12 (range, 4-43)	Improvement in 63%
Freund *et al*., 2016	1	Plasma exchange, IVIg, rituximab	8	Partial improvement
Govert *et al*., 2016	1	Steroids, IVIg	12	Improvement
van Sonderen *et al*., 2016	38	Steroids, IVIg, plasma exchange, cyclophosphamide, rituximab, thymectomy	36 (range, 3-168)	Improvement in 91% Death in 0.1% Relapse in 25%
Gadoth *et al*., 2017	95* (77 LGI1 positive, 15 CASPR2 positive, 3 dual positive)	Steroids, IVIg, mycophenolate	35 (range, 7-456)	Improvement in 73% Relapse in 59%
Kannoth *et al*., 2017	3	Steroids, cyclophosphamide	Not available	Improvement in 100%
Boyko *et al*., 2020	667	Not available	Not available	Not available
Current study	8	Steroids, plasma exchange	19.71 (range, 2-52)	Improvement in 7/8 Death in 1/8 (had underlying thymoma) Relapse in 1/8

IVIg: Intravenous immunoglobulin. *Studies included patients with LGI1 and/or CASPR2 antibody positive patients

plasma exchange, IVIg, steroid-sparing agents (azathioprine, mycophenolate, cyclophosphamide, cyclosporine, rituximab), and immunadsorption [Table 5].

Good outcome has been reported in 62–91% of patients in previous studies. In the present study too, majority of the patients improved as documented by mRS. The mRS is a widely used clinical outcome measure for objective documentation of the extent of disability, which was initially developed for stroke but has been subsequently used for other neurological disorders.[28] Since there are no disease-specific scales for CASPR antibody-associated neurological disorder, we used the mRS for objective documentation of response to treatment and outcome at follow-up. The mRS has been used in previous studies of CASPR2 antibody-associated neurological illness.[15,17] Poor outcome and death are usually related to underlying malignancy.[3,11,16] In our cohort, one patient who had underlying thymoma and associated myasthenia gravis died. Removal of underlying tumor in patients who did not respond to immunotherapy has been shown to be beneficial.[15]

We administered immunotherapy in two phases, that is, intensive phase during the acute symptomatic period where intravenous methyl prednisolone was given with or without plasma exchange, followed by maintenance phase where pulsed intravenous methyl prednisolone was continued to prevent relapses. Relapses in CASPR2 antibody-associated neurological disorders are uncommonly reported and range from 6.8% to 25% and may occur as late as 7 years after the initial episode.[15-17] Relapses may be related to inadequate immunotherapy of first episode or reduction/cessation of immunotherapy as was noted in patient 8 in the present study. Relapses can involve sites of the neuraxis different from that involved in the initial attacks. Nonparaneoplastic CASPR2 antibody-associated illness may preferentially have a monophasic course.[24] We used both clinical and serological response as criteria to taper or stop treatment. We arbitrarily tapered steroids after 1 year and stopped treatment after 3 years if the clinical and serological remission was sustained. In other immune-mediated diseases like myasthenia gravis[29] and systemic lupus erythematosus (SLE),[30] duration of therapy is usually determined by clinical improvement and when remission is achieved, immunotherapy is tapered to the lowest effective dose possible. There is no consensus on the role of using serological markers such as acetylcholine receptor antibodies in myasthenia gravis or antinuclear antibodies (ANA) in SLE to determine response to treatment. It is generally not recommended to use serological markers in isolation to make therapeutic decisions.[29,30] A similar strategy may be useful in treating patients with CASPR2 antibody-associated disease, where the decision to taper immunotherapy is determined predominantly by clinical improvement or by a combination of clinical and antibody status rather than antibody status alone.

In conclusion, CASPR2 antibody-associated neurological disorder is uncommon and data regarding response to treatment and long-term outcome in these patients, especially from India, are limited. Our study ascertained the clinical profile and response to immunotherapy with near total improvement in a cohort of patients with CASPR2 antibody-associated disease. CASPR2 antibody-associated neurological disease should be suspected in any patient with insomnia, encephalopathy, autonomic dysfunction, pain, and/or peripheral nerve hyperexcitability with a normal neuroimaging. Diagnosis is established by serum antibody positivity but patients with CSF antibody positivity may present with features of limbic encephalitis. Screening for underlying malignancy is mandatory as it impacts prognosis. These patients respond well to immunotherapy but regular follow-up is important to identify relapse as early as possible. The present study, though small, provides data on the therapeutic response to immunomodulation in a cohort of patients who were seen and followed up in a single neurology unit of a tertiary care university hospital. Further studies with longer duration of follow-up are needed to understand whether these patients attain true remission or the disease activity is merely suppressed with treatment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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