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Review Article

LGI1 and CASPR2 autoimmunity in children: Systematic literature review and report of a young girl with Morvan syndrome

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ABSTRACT

Leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) neurological autoimmunity in adults has been associated with various clinical syndromes involving central, peripheral and autonomic nervous system, while data in children is limited. We perform the first systematic literature review on paediatric LGI1 and CASPR2 autoimmunity, with focus on clinical data, in order to contribute to the definition of clinical features of LGI1 and CASPR2 autoimmunity in paediatric age and favour early diagnosis. Additionally, we report the youngest-to-date case of Morvan syndrome.

We identified 37 published paediatric cases of LGI1 and/or CASPR2 autoimmunity. Most frequent syndromes were encephalitis in LGI1-positive and isolated epilepsy in CASPR2-positive children, while syndromes with predominant peripheral symptoms were most frequent in double-positive children. With the limitations imposed by the low number of cases, differences to published adult cohorts included: absence of faciobrachial dystonic seizures and hyponatremia in patients with LGI1-positive encephalitis; slightly higher proportion of isolated epilepsy syndromes in CASPR2-positive patients; absence of tumour in the whole cohort.

1. Introduction

Leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) were identified in 2010 as the main antigens within the voltage-gated potassium channel-complex (VGKC) (Lai et al., 2010; Irani et al., 2010). LGI1 and CASPR2 antibodies have been mostly reported in adult patients so far, in association with different clinical pictures. Limbic encephalitis is one of the most common clinical presentation in both LGI1 and CASPR2 autoimmunity (Binks et al., 2018); in LGI1 encephalitis, pathognomonic faciobrachial dystonic seizures have been reported in about 26–71% of patients, and hyponatremia in about 65% (Gadoth et al., 2017; van Sonderen et al., 2016; van Sonderen et al., 2017). Other clinical pictures associated with LGI1 and CASPR2 antibodies include isolated epilepsy (described both with LGI1 and CASPR2 antibodies, less frequent in LGI1-CASPR2 double-positive patients), Morvan syndrome, neuromyotonia (both more frequent in CASPR2-positive and in double-positive patients) (Lai et al., 2010; Irani et al., 2010) and other less common syndromes. Association with tumour occurs in up to 11–13% of cases with LGI1 (most frequently thymoma; other: thyroid, lung, renal, ovarian, prostate, skin, colon tumour and others) (van Sonderen et al., 2016; Gadoth et al., 2017), in up to 20–32% with CASPR2 antibodies (most frequently thymoma; other: prostate, skin, thyroid tumours and others), and in up to 44–46% in double-positive patients (generally thymoma; other: melanoma, prostate) (Lai et al., 2010; Irani et al., 2010; Gadoth et al., 2017; Binks et al., 2018).

LGI1 and CASPR2 autoimmunity has been infrequently reported in children, and the clinical spectrum in this age has not been completely

Abbreviations: ANS, autonomic nervous system; CASPR2, contactin-associated protein-like 2; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; LGI1, leucine-rich glioma-inactivated protein 1; mRS, modified Rankin Scale; PNS, peripheral nervous system; VGKC, voltage-gated potassium channel-complex

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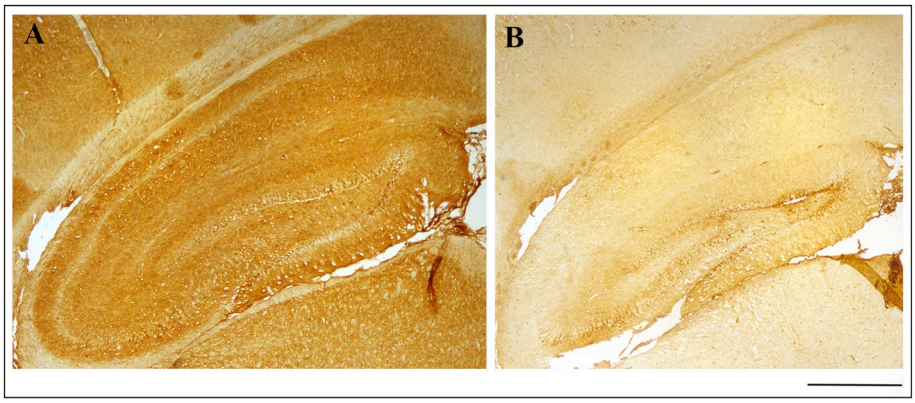

Fig. 1. Immnohistochemical staining of neuronal antibodies in rat frozen brain sections, A. Representative picture of the presence of anti-neuropil antibodies in the serum of the paediatric patient. B. Representative picture of a patient serum negative for antineuronal antibodies (negative control). Pictures taken at 5× magnification (scale bar:500 um).

defined yet. We hereby describe a new case of double-positive serum and cerebrospinal fluid (CSF) LGI1 and CASPR2 antibodies in an infant girl with Morvan syndrome, and carry out a systematic literature review on LGI1 and CASPR2 autoimmunity in paediatric age with focus on clinical data.

2. Methods

We present a new clinical case of a 12-month-old female with Morvan syndrome with positive serum and CSF CASPR2 and LGI1 antibodies, and the results of a literature review of paediatric patients (≤18 years) with CASPR2 and/or LGI1 antibodies. The literature search was carried out in Pubmed, uptodate to 15.07.2019, with the following search keys: '(LGI1 or leucine-rich glioma inactivated 1) and (children or pediatric)', '(CASPR2 or contactin-associated protein 2) and (children or pediatric)', 'Morvan syndrome'. Retrieved articles were searched manually to select paediatric patients (0–18 years) with positive CASPR2 and/or LGI1 antibodies with available individual data, and relevant information was extracted with focus on clinical information. Clinical data was categorised in two levels: clinical syndrome (the overall clinical diagnosis, as provided by the authors; i.e.: encephalitis, epilepsy, Morvan syndrome, etc.) and clinical symptoms (individual symptoms within a clinical syndrome, according to the clinical description available in the original report; i.e. encephalopathy, seizures, psychiatric symptoms, dysautonomia, pain, etc.). Clinical syndromes in the acute phase were categorised as follows: predominantly central nervous system (CNS) syndromes (with/without minor peripheral (PNS) and/or autonomic (ANS) nervous system symptoms) (i.e.: encephalitis, epilepsy); syndromes with mixed CNS and PNS involvement (with/without ANS symptoms) (i.e.: Morvan syndrome); and syndromes with predominant PNS symptoms (with/without ANS involvement) (i.e.: acquired neuromyotonia, Guillain-Barré syndrome). As regards clinical symptoms, for the distinction between encephalitis and epilepsy we considered the diagnosis of isolated epilepsy when it was formulated as such by the authors of the original papers, and in particular in case of recurrent seizures without associated features typical of encephalitis.

Neurological severity in the acute phase and outcome at last follow-up were assessed retrospectively via the modified Rankin Scale (mRS) (van Swieten et al., 1988) by one of the main authors, wherever not provided in the original article.

3. Results

3.1. Illustrative case

A 12-month-old female presented with a two-week history of non-purulent conjunctivitis, followed by photophobia, signs of respiratory infection, skin rash, severe hyperhydrosis, neuropathic itching, irritability, insomnia, fatigue and decreased level of consciousness, with regression of motor milestones. Physical examination at admission revealed tachycardia and arterial hypertension.

Initial blood chemistry only showed hyperreninemia. Urinary catecholamines, thyroid function and thyroid peroxidase antibodies were normal. Brain MRI, total body PET-MRI scan, abdominal ultrasound, electroencephalography (EEG) and electromyography (EMG) were normal. Extended microbiology and oncology screening on blood and CSF was unremarkable. CSF analysis revealed normal cell count, protein and glucose level, with negative oligoclonal bands. Neural antibody screening revealed LGI1 (serum titer 1:1280, CSF titer 1:2, specific antibody index 1.3) and CASPR2 antibodies (serum titer 1:640, CSF titer 1:2 specific antibody index 2.6), done by a commercial cell-based assay (Euroimmun, Lubeck, Germany) with a modified protocol (Bien et al., 2017). Anti-VGKC complex antibodies by radioimmunoassay were also strongly elevated (588 pmol/L, normal values < 85 pmol/L). The girl was diagnosed with Morvan syndrome. Repeat LGI1 and CASPR2 antibodies four weeks after onset (before immune therapy) came back negative in CSF and with partly decreased titers in serum (LGI1 antibodies 1:160, CASPR2 antibodies still at 1:640) (Fig. 1).

Supportive treatment with intravenous hydration, antihistaminic drugs and three antihypertensive treatments were used (amlodipine, atenolol, captopril). Encephalopathy gradually improved spontaneously a few weeks after onset, although with persistence of the remaining symptoms. Immune therapy was started one month after onset of symptoms: high-dose intravenous methylprednisolone (30 mg/kg/day for 5 days) followed by oral corticosteroid taper with prednisone (initial dose 1 mg/kg/day, slowly tapered over 5 months), and intravenous immunoglobulin (2 g/kg in 5 days, started one day after completion of high-dose methylprednisolone). While the girl had started to improve spontaneously three weeks after onset, before immune therapy, this treatment led to further significant and steady improvement of encephalopathy, dysautonomia, and hyperhidrosis.

At discharge, two months after onset, the infant showed normal neurological exam, with almost complete resolution of CNS and autonomic symptoms, except for the persistence of mild hyperhidrosis, which resolved about 2 weeks after discharge. At last follow-up 12 months after disease onset, serum LGI1 and CASPR2 antibodies were negative (< 1:20; anti-VGKC complex antibodies 18 pmol/L); neurological examination and developmental milestones were normal.

3.2. Literature review

Results of the literature review on paediatric patients with CASPR2 and/or LGI1 neurological autoimmunity are presented in Table 1 (further details are provided in Supplementary Table 1). 37 published paediatric patients with CASPR2 and/or LGI1 autoimmunity were identified (Suleiman et al., 2013; Kim et al., 2014; Steriade et al., 2014; Sunwoo et al., 2015; Hacohen et al., 2015; Erer Özbek et al., 2015;

Wright et al., 2016; Incecik et al., 2016; AlHakeem et al., 2016; Janas-Kozik et al., 2017; Nikolaus et al., 2018; Schimmel et al., 2018; López-Chiriboga et al., 2018; Surana et al., 2019; Boesen et al., 2019). According to the inclusion criteria, cases with unavailable individual data were excluded (i.e. cases included in large cohorts with only pooled data provided) (de Bruijn et al., 2019; Deng et al., 2019).

37.8% (14/37) patients had LGI1 antibodies, 37.8% (14/37) had CASPR2 antibodies, and 24.3% (9/37) patients were double-positive to LGI1 and CASPR2 antibodies.

3.2.1. Demographics

Overall 56.8% (21/37) of patients were male; this proportion was higher in double-positive patients (7/9, 77.8%) and in the CASPR2-positive subgroup (8/14, 57.1%), as compared to LGI1-positive patients

Table 1
Results of the literature review on neurological disorders associated to LGI1 and CASPR2 autoimmunity in children.

	LGI1 (*n* = 14)	CASPR2 (n = 14)	Double-positive (*n* = 9)	Total cohort (*n* = 37)
Demograhics				
Proportion of males	6/14 (42.9%)	8/14 (57.1%)	7/9 (77.8%)	21/37 (56.8%)
Age at onset (years)	Median 13, mean 11.6, range 5–18 (d.a.: 14/14)	Median 8, mean 7.2, range 0.5–13 (d.a.: 14/14)	Median 7, mean 8.9, range 2–16 (d.a.: 9/9)	Median 8.9, mean 9.3, range 0.5–18 (d.a.: 37/37)
Clinical syndromes				
Predominantly CNS syndromes	11/14 (78.6%)	11/14 (78.6%)	1/9 (11.1%)	23/37 (62.2%)
Encephalitis[a]	10/14 (71.4%)	2/14 (14.3%)	1/9 (11.1%)	13/37 (35.1%)
Isolated epilepsy, epileptic encephalopathy or seizure disorder	0/14 (0%)	8/14 (57.1%)	0/9 (0%)	8/37 (21.6%)
Other[b]	1/14 (7.1%)	1/14 (7.1%)	0/9 (0%)	2/37 (5.4%)
Mixed CNS + PNS syndrome (+/2ANS)	2/14 (14.3%)	2/14 (14.3%)	3/9 (33.3%)	7/37 (18.9%)
Morvan syndrome	0/14 (0%)	0/14 (0%)	3/9 (33.3%)	3/37 (8.1%)
Other	2/14 (14.3%)	2/14 (14.3%)	0/9 (0%)	4/37 (10.8%)
Predominantly PNS syndrome (+/2ANS)	1/14 (7.1%)	1/14 (7.1%)	5/9 (55.6%)	7/37 (18.9%)
Acquired neuromyotonia	0/14 (0%)	0/14 (0%)	3/9 (33.3%)	3/37 (8.1%)
Guillain-Barré syndrome	0/14 (0%)	1/14 (7.1%)	1/9 (11.1%)	2/37 (5.4%)
Other	1/14 (7.1%)	0/14 (0%)	1/9 (11.1%)	2/37 (5.4%)
Symptoms and disease severity				
Encephalopathy	10/14 (71.4%)	5/14 (35.7%)	3/9 (33.3%)	19/37 (51.4%)
Seizures	8/14 (57.1%)	7/14 (50%)	2/9 (22.2%)	17/37 (45.9%)
Psychiatric changes	9/14 (64.3%)	1/14 (7.1%)	3/9 (33.3%)	14/37 (37.8%)[c]
Sleep disturbances	4/14 (28.6%)	1/14 (7.1%)	2/9 (22.2%)	8/37 (21.6%)
Movement disorder	3/14 (21.4%)	1/14 (7.1%)	1/9 (11.1%)	5/37 (13.5%)
Memory impairment	2/14 (14.3%)	1/14 (7.1%)	0/9 (0%)	4/37 (10.8%)
Dysautonomia	5/14 (35.7%)	0/14 (0%)	4/9 (44.4%)	10/37 (27%)
Weight loss	2/14 (14.3%)	0/14 (0%)	4/9 (44.4%)	6/37 (16.2%)
Pain/Cramps	4/14 (28.6%)	3/14 (21.4%)	6/9 (66.7%)	13/37 (35.1%)
Neuromyotonia/Myokimia	0/14 (0%)	0/14 (0%)	6/9 (66.7%)	6/37 (16.2%)
Weakness	1/14 (7.1%)	1/14 (7.1%)	4/9 (44.4%)	6/37 (16.2%)
Sensory disturbances	1/14 (7.1%)	0/14 (0%)	1/9 (11.1%)	2/37 (5.4%)
Other PNS symptoms	0/14 (0%)	2/14 (14.3%)	3/9 (33.3%)	6/37 (16.2%)
Worst mRS in the acute phase	Median 3, mean 3.3, range 3–5 (d.a.: 14/14)	Median 3, mean 3.3, range 3–4 (d.a.: 10/14)	Median 4, mean 3.3, range 1–4 (d.a.: 9/9)	Median 3, mean 3.3, range 1–5 (d.a.: 33/37)
mRS 4–5	5/14 (35.7%)	3/10 (30%)	5/9 (55.6%)	13/33 (39.4%)
Intensive care unit	2/14 (14.3%)	0/14 (0%)	0/9 (0%)	2/37 (5.4%)
Investigations				
Abnormal brain MRI	6/13 (46.1%)	3/8 (37.5%)	1/6 (16.7%)	10/27 (37%)
Limbic	4/13 (30.8%)	0/8 (0%)	0/6 (0%)	4/26 (15.4%)
Extralimbic	2/13 (15.4%)	3/8 (37.5%)	1/6 (16.7%)	6/26 (23.1%)
Unilateral	2/13 (15.4%)	1/8 (12.5%)	0/6 (0%)	3/27 (11.1%)
Bilateral	4/13 (30.8%)	2/8 (25%)	1/6 (16.7%)	7/27 (25.9%)
Abnormal spine MRI	0/1 (0%)	1/3 (33.3%)	1/6 (16.7%)	2/10 (20%)
Abnormal EEG	6/11 (54.5%)	6/6 (100%)	1/2 (50%)	13/19 (68.4%)
Slowing	2/11 (18.2%)	6/6 (100%)	1/2 (50%)	9/19 (47.4%)
Epileptiform discharges	4/11 (36.4%)	4/6 (66.7%)	0/2 (0%)	8/19 (42.1%)
Abnormal EMG	1/3 (33.3%)	n.a.	6/8 (75%)	7/11 (63.6%)
Abnormal CSF	5/11 (45.4%)	4/5 (80%)	3/5 (60%)	12/21 (57.1%)
Pleocytosis > 4 cells/uL	2/11 (18.2%)	2/5 (40%)	1/5 (20%)	5/21 (23.8%)
Hyperpreoteinorrachia > 45 mg/dL	2/11 (18.2%)	4/5 (80%)	2/5 (40%)	8/21 (38.1%)
Positive oligoclonal bands	4/5 (80%)	n.a.	0/1 (0%)	4/7 (57.1%)
Hyponatremia	0/14 (0%)	0/14 (0%)	1/9 (11.1%)	1/37 (2.7%)
Immune therapy	11/14 (78.6%)	5/14 (35.7%)	5/9 (55.6%)	21/37 (56.8%)
Intravenous methylprednisolone	8/14 (57.1%)	2/43 (14.3%)	3/9 (33.3%)	13/37 (35.1%)
Oral prednisone	5/14 (35.7%)	0/14 (0%)	2/9 (22.2%)	7/37 (18.9%)
Intravenous immunoglobulin	10/14 (71.4%)	4/14 (28.6%)	4/9 (44.4%)	18/37 (48.6%)
Therapeutic plasma exchange	1/14 (7.1%)	1/14 (7.1%)	0/9 (0%)	2/37 (5.4%)
Mycophenolate mofetil	1/14 (7.1%)	0/14 (0%)	0/9 (0%)	1/37 (2.7%)
Azathioprine	1/14 (7.1%)	0/14 (0%)	0/9 (0%)	1/37 (2.7%)
Methotrexate	0/14 (0%)	0/14 (0%)	1/9 (11.1%)	1/37 (2.7%)

(*continued on next page*)

Table 1 (*continued*)

	LGI1 (n = 14)	CASPR2 (n = 14)	Double-positive (n = 9)	Total cohort (n = 37)
Outcome				
Length of follow-up (months)	Median 12.5, mean 20.6, range 2–60 (d.a.: 12/14)	Median 46.5, mean 60.2, range 6–192 (d.a.: 8/14)	Median 7, mean 14.6, range 1–50 (d.a.: 9/9)	Median 16, mean 29.6, range 1–192 (d.a.: 29/37)
Relapses	2/14 (14.3%)	2/7 (28.3%)	1/9 (11.1%)	5/30 (16.7%)
mRS at last follow-up	Median 1, mean 0.9, range 0–2 (d.a.: 14/14)	Median 1, mean 1.2, range 0–3 (d.a.: 12/14)	Median 1, mean 1, range 0–3 (d.a.: 9/9)	Median 1, mean 1, range 0–3 (d.a.: 35/37)
mRS 0	3/14 (21.4%)	3/12 (25%)	2/9 (22.2%)	8/35 (22.8%)
mRS 1	9/14 (64.3%)	5/12 (41.7%)	6/9 (66.7%)	20/35 (57.1%)
mRS 2	2/14 (14.3%)	2/12 (16.7%)	0/9 (0%)	4/35 (11.4%)
mRS 3	0/14 (0%)	2/12 (16.7%)	1/9 (11.1%)	3/35 (8.6%)
Seizures at last follow-up; AED at last follow-up	1/12 (8.3%); 3/11 (27.3%)	7/12 (58.3%); 6/9 (66.7%)	0/9 (0%); 0/9 (0%)	8/33 (24.2%); 9/28 (33.3%)

Legend: AED: antiepileptic drug; ANS: autonomic nervous system; CNS: central nervous system; CSF: cerebrospinal fluid; d.a.: data available; EEG: electroencephalography; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; PNS: peripheral nervous system; +/−: with/without.

[a] The subgroup of patients with encephalitis includes both patients diagnosed with 'limbic encephalitis' and patients diagnosed more generically with 'encephalitis' according to the original papers. Among patients with encephalitis, one 18-year old LGI1-positive patient had encephalitis with cerebellar degeneration (Steriade et al., 2014).

[b] Other predominantly CNS syndromes were: 1 LGI1-positive patient with hyperkinetic movement disorder (Erer Özbek et al., 2015), and 1 CASPR2-positive patient with Kleine-Levine syndrome (Boesen et al., 2019).

[c] Psychiatric symptoms were (in 10/14 patients with psychiatric symptoms and available data): hallucinations, delusions or psychosis in 5/10, depression, emotional lability or mood disorder in 5/10, anxiety in 2/10, agitation in 2/10, aggressive behavior in 3/10, and confusion or disorientation in 3/10; inattention, suicidal thoughts, kleptomania, panic attacks, hyperactivity, increase stubbornness, disinhibited behaviours were reported in 1 patient each.

(6/14, 42.9%). Median age at onset was 8.9 years (range 0.5–18), slightly higher in LGI1-positive patients than in CASPR2-positive and in double-positive patients (13 versus 8 versus 7 years, respectively).

3.2.2. Clinical syndromes

Predominantly CNS syndromes (with/without minor PNS and/or ANS involvement) were the most frequent clinical syndromes overall (23/37, 62.2%), including encephalitis (13/37, 35.1%), epilepsy, epileptic encephalopathy or seizure disorder (8/37, 21.6%), and other (2/37, 5.4%). Syndromes with mixed CNS and PNS involvement (with/without ANS symptoms) were described in 18.9% (7/37), including Morvan syndrome (3/37, 8.1%) and other (4/37, 10.8%). PNS syndromes (with/without ANS involvement) were described in 18.9% (7/37), including acquired neuromyotonia (3/37, 8.1%), Guillain-Barré syndrome (2/37, 5.4%), and other (2/37, 5.4%).

Syndromes with predominant CNS involvement were the most frequent clinical syndromes among the two subgroups of LGI1-positive and CASPR2-positive patients (11/14, 78.6% each). In particular, encephalitis was most frequent in LGI1-positive patients (10/14, 71.4%), and isolated epilepsy, epileptic encephalopathy or seizure disorder were most frequent in CASPR2-positive patients (8/14, 57.1%).

Whereas, among the 9 double-positive patients, syndromes with predominant PNS symptoms were most frequent (5/9, 55.6%; especially acquired neuromyotonia, 3/9, 33.3%), followed by syndromes with mixed CNS and PNS involvement (3/9, 33.3%; Morvan syndrome in 3/9, 33.3%).

3.2.3. Clinical symptoms

Encephalopathy (19/37, 51.4%), seizures (17/37, 45.9%) and psychiatric disturbances (14/37, 37.8%) were the most frequently described symptoms overall. Both encephalopathy and psychiatric disturbances were most frequent among LGI1-positive patients (10/14, 71.4% and 9/14, 64.3%, respectively). While isolated epilepsy as a syndrome was most frequent in CASPR2-positive patients (see above), seizures as a symptom (e.g. in the context of encephalitis, isolated epilepsy or other), were similarly represented among LGI1-positive and CASPR2-positive patients (8/14, 57.1% and 7/14, 50% respectively), and least frequent in double-positive patients (2/9, 22.2%). Among the 10 patients with LGI1 encephalitis, 80% (8/10) had psychiatric disturbances, 80% (8/10) had seizures (none had faciobrachial dystonic seizures), 30% (3/10) had sleep disturbances, 30% (3/10) had dysautonomia, 20% (2/10) had movement disorder, and 20% (2/10) had memory impairment (Table 2). Both the 2 patients with CASPR2 encephalitis had seizures (2/2, 100%), whereas psychiatric changes and memory impairment were reported in one patient each (1/2, 50%), and dysautonomia and sleep disturbances were not reported (Table 2).

Table 2
Results of the literature review on neurological disorders associated to LGI1 and CASPR2 autoimmunity in children: main data in the subgroups with LGI1-positive and CASPR2-positive encephalitis.

	LGI1-positive encephalitis (n = 10)	CASPR2-positive encephalitis (n = 2)
Clinical symptoms and disease severity		
Encephalopathy	9/10 (90%)	2/2 (100%)
Seizures	8/10 (80%)	2/2 (100%)
Psychiatric changes	8/10 (80%)	1/2 (50%)
Sleep disturbances	3/10 (30%)	0/2 (0%)
Movement disorder	2/10 (20%)	0/2 (0%)
Memory impairment	2/10 (20%)	1/2 (50%)
Dysautonomia	3/10 (30%)	0/2 (0%)
Worst mRS in the acute phase	Median 3, mean 3.5, range 2–5 (d.a.: 10/10)	Median 3.5, mean 3.5, range 3–4 (d.a.: 2/2)
mRS 4–5	4/10 (40%)	1/2 (50%)
Intensive care unit	1/10 (10%)	0/2 (0%)
Investigations		
Abnormal brain MRI	6/10 (60%)	2/2 (100%)
Abnormal EEG	6/9 (66.7%)	2/2 (100%)
Abnormal CSF	5/9 (55.6%)	1/1 (100%)
Hyponatremia	0/9 (0%)	0/2 (0%)
Immune therapy		
Any immune therapy	9/10 (90%)	2/2 (100%)
Outcome		
Length of follow-up (months)	Median 18, mean 26.9, range 3–60 (d.a.: 8/10)	Median 18, mean 18, range 18–18 (d.a.: 2/2)
Relapses	1/10 (10%)	0/2 (0%)
mRS at last follow-up	Median 1, mean 0.9, range 0–2 (d.a.: 10/10)	Median 1, mean 1, range 1–1 (d.a.: 2/2)
Seizures at last follow-up; AED at last follow-up	1/8 (12.5%); 3/7 (42.9%)	1/2 (50%); 1/1 (100%)

Legend: AED: antiepileptic drug; CSF: cerebrospinal fluid; EEG: electroencephalography; MRI: magnetic resonance imaging; mRS: modified Rankin Scale.

Autonomic disturbances were reported in overall 27% (10/37) patients, most frequently in double-positive patients (4/9, 44.4%) and in LGI1-positive patients (5/14, 35.7%). Pain or cramps occurred in overall 35.1% (13/37), neuromyotonia in 16.1% (6/37), and weakness in 16.1% (6/37), all more frequent in double-positive patients (6/9, 66.7%; 6/9, 66.7%; and 4/9, 44.4% respectively). No tumours were reported.

3.2.4. Disease severity

Median mRS in the acute phase was 3 (mean 3.3, range 1–5; data available in 33/37), highest in double-positive patients (median mRS 4). 5.4% (2/37) patients, both LGI1-positive, required admission to the intensive care unit.

3.2.5. Investigations

Abnormal brain MRI was reported in 37% (10/27), abnormal spine MRI in (2/10, 20%), abnormal EEG in 68.4% (13/19), abnormal EMG in 63.6% (7/11), and abnormal CSF in 57.1% (12/21). Mild hyponatremia was reported only in 1 double-positive patient with Morvan syndrome.

3.2.6. Immune therapy

Overall, 56.8% (21/37) of patients received immune therapy, more frequently in the LGI1-positive subgroup (11/14, 78.6%) than in double-positive (5/9, 55.6%) and in CASPR2-positive patients (5/14, 35.7%). Most frequent agents were intravenous methylprednisolone (13/37, 35.1%), oral prednisone (7/37, 18.9%), intravenous immunoglobulin (18/37, 48.6%) and therapeutic plasma exchange (2/37, 5.4%). None of the patients received second-line immune therapies (i.e. rituximab or cyclophosphamide), whereas 8.1% (3/37) received steroid sparers (mycophenolate mofetil, azathioprine, or methotrexate).

As regards the subgroup of patients who did not receive immune therapy (16/37, 43.2%) (Supplementary Table 2) compared to the whole literature cohort, these had less frequently encephalitis (1/16, 6.3% versus 13/37, 35.1%), more frequently isolated epilepsy (8/16, 50% versus 8/37, 21.6%), and slightly lower disease severity in the acute phase (mRS 4–5: 1/12, 8.3% versus 13/33, 39.4%). Although median length of follow-up was slightly shorter among patients who did not receive immune therapy compared to the whole literature cohort (10.5 months versus 16 months), patients not treated with immune therapy had slightly worse mRS (mRS 2–3 in 5/14, 35.7% versus 7/35, 20%) and higher proportion of seizures at last follow-up (6/14, 42.9% versus 8/33, 24.2%), despite less relapsing disease (0/9, 0% versus 5/30, 16.7%).

3.2.7. Outcome

At median follow-up of 16 months (mean 29.6, range 1–192; data available in 29/37), relapses occurred in 16.7% (5/30), most frequently in CASPR2-positive patients (2/7, 28.3%, although this subgroup also had the longest median follow-up: 46.5 months). Median mRS at last follow-up was 1 (mean 1, range 0–3; data available in 35/37), and 24.2% of patents had ongoing seizures (8/33), most frequently in the CASPR2-positive subgroup (7/12, 58.3%).

4. Discussion

We describe the youngest-to-date LGI1- CASPR2 double-positive case with Morvan syndrome and present the results of the first systematic literature review on LGI1 and CASPR2 autoimmunity in children.

Our 12-month-old girl with Morvan syndrome presented with CNS (insomnia, decreased level of consciousness, irritability), PNS (neuropathic itching) and ANS symptoms (hyperhidrosis, tachycardia, arterial hypertension) associated with serum and CSF LGI1 and CASPR2 antibodies. The syndrome is usually described in adults, and to our knowledge only 3 other paediatric patients with Morvan syndrome and available antibody results were published (Nikolaus et al., 2018; López-Chiriboga et al., 2018) (2/3 females; age range 6–16 years), all 3 double-positive for LGI1 and CASPR2 antibodies. Similarly to one of these patients (Nikolaus et al., 2018), we detected CASPR2 antibodies in CSF in addition to serum because of the high serum titer, which is rare for Morvan syndrome (Joubert et al., 2016). Another unique feature of our case is the female gender. Indeed, Morvan syndrome is very rare among females, being the male to female ratio 19:1 (Masood and Sitammagari, 2019). The loss of male predominance among the 3 previously published paediatric Morvan syndrome cases (Nikolaus et al., 2018; López-Chiriboga et al., 2018) might possibly represent an age-dependent feature of the syndrome, similarly to the relative attenuation of the female predominance among children with anti-NMDAR encephalitis as compared to adults (Titulaer et al., 2013).

Our literature review on LGI1 and CASPR2 autoimmunity in children disclosed only 37 published paediatric cases of LGI1 and/or CASPR2 autoimmunity, with age at onset ranging between 0.5 and 18 years (Suleiman et al., 2013; Kim et al., 2014; Steriade et al., 2014; Sunwoo et al., 2015; Hacohen et al., 2015; Erer Özbek et al., 2015; Wright et al., 2016; Incecik et al., 2016; AlHakeem et al., 2016; Janas-Kozik et al., 2017; Nikolaus et al., 2018; Schimmel et al., 2018; López-Chiriboga et al., 2018; Surana et al., 2019; Boesen et al., 2019). Our paediatric literature cohort reflected the known male predominance of LGI1 and CASPR2 autoimmunity in adult patients (Binks et al., 2018; Gadoth et al., 2017), especially marked as regards the CASPR2-positive (van Sonderen et al., 2017) and the double-positive subgroups; this is a distinguishing feature compared to other autoimmune encephalitis where female gender is predominant, such as anti-NMDAR encephalitis (Titulaer et al., 2013).

Similarly to data in adult patients, clinical presentations in our paediatric literature cohort included different clinical syndromes with variable involvement of CNS, PNS and ANS, with a certain degree of overlap between the three subgroups of LGI1-positive, CASPR2-positive and double-positive patients (Binks et al., 2018). According to our review, most frequent clinical syndromes among LGI1-positive and CASPR2-positive patients were syndromes with predominant CNS involvement (with or without minor PNS and/or ANS symptoms): encephalitis (including limbic encephalitis) in LGI1-positive patients, in agreement with published adult cohorts (Gadoth et al., 2017), and isolated epilepsy syndromes (including epileptic encephalopathy or seizure disorders) in CASPR2-positive patients, slightly more often so compared to adults (57.1% versus 18%–49%, respectively) (Gadoth et al., 2017; Klein et al., 2013). Moreover, seizures were similarly represented in CASPR2-positive and in LGI1-positive cases in our paediatric literature cohort, while a higher frequency of seizures in LGI1-positive cases compared to CASPR2-positive patients is described in adults (Irani et al., 2010; Gadoth et al., 2017). Interestingly, faciobrachial dystonic seizures, uniquely associated to LGI1 antibodies (Irani et al., 2011; Irani et al., 2013) and reported in about 26–71% of LGI1-positive adult patients with encephalitis (Gadoth et al., 2017; van Sonderen et al., 2016; van Sonderen et al., 2017), were not reported in our literature cohort, not even in the patients described in the original articles as LGI1-positive limbic encephalitis (Incecik et al., 2016; Janas-Kozik et al., 2017; Schimmel et al., 2018; López-Chiriboga et al., 2018). The lack of hyponatremia (apart from 1 double-positive patient with Morvan syndrome) (Nikolaus et al., 2018) is another difference of our paediatric literature cohort to adult series with LGI1 limbic encephalitis or with double-positivity (Gadoth et al., 2017). Overall, proportion of patients with ongoing seizures at last follow-up in our literature cohort appeared higher than in other paediatric cohorts with autoimmune encephalitis, such as anti-*N*-methyl-D-aspartate receptor encephalitis (24.2% versus 3.4–5.5%, respectively) (Sartori et al., 2015; Spatola and Dalmau, 2017; Nosadini et al., 2019), and was highest in the CASPR2-positive subgroup (66.7%) in our literature cohort.

As regards other CNS symptoms, memory impairment was relatively rare in our paediatric literature cohort compared to adult series (Irani

et al., 2010; Gadoth et al., 2017), possibly due to the relatively higher difficulty of detecting this symptom in children than in older patients, while psychiatric changes were most frequently reported in LGI1-positive and double positive patients, similarly to adults (Gadoth et al., 2017).

On the other hand, our paediatric literature cohort confirms the predominance of PNS involvement among double-positive patients as previously described in adult series (Gadoth et al., 2017; Klein et al., 2013) also confirmed by the high frequency of EMG abnormalities. In this subgroup of double-positive patients, most frequent clinical syndromes included mixed CNS and PNS symptoms, such as Morvan syndrome, and predominant PNS involvement, such as in acquired neuromyotonia. Dysautonomia, weight loss, pain or cramps, neuromyotonia, weakness and other PNS symptoms were most frequently reported in double-positive patients in our literature cohort, similarly to adult patients (Binks et al., 2018). These symptoms were similarly represented in the LGI1-positive and in the CASPR2-positive subgroups (apart from dysautonomias and weight loss being more frequent in LGI1-positive patients); whereas, neuromyotonia, neuropathic pain, insomnia, dysautonomia and weight loss were more frequent in CASPR2-positive patients than in LGI1-positive patients in literature data in adults (Irani et al., 2010; Klein et al., 2012; Binks et al., 2018).

Immune therapy has been shown to be beneficial in adult patients with LGI1 (Irani et al., 2010; Irani et al., 2011; Klein et al., 2012) and CASPR2 antibodies (Sunwoo et al., 2015; Nosadini et al., 2015; Lancaster et al., 2011), although it was used only in 56.8% of our paediatric literature cohort, most frequently in LGI1-positive patients; despite this, outcome was generally good. The low rate of use of immune therapy, including the complete lack of use of second-line treatments such as rituximab or cyclophosphamide, may be at least partly due to the relatively low disease severity in the acute phase (median mRS 3; admission to the intensive care unit 5.4%), especially in the subgroup that did not receive immune therapy (Supplementary Table 1). Additionally, a delay in the recognition of the disease might have played a role too, in view of the extreme rarity of LGI1 and CASPR2 autoimmunity in children. Although they had slightly shorter length of follow-up, patients not treated with immune therapy had slightly worse mRS and higher proportion of seizures at last follow-up compared to the whole literature cohort, despite less relapsing disease.

Overall, based on the limited number of paediatric cases published so far, LGI1 and/or CASPR2 autoimmunity appears to be rare in children, although its incidence is hard to estimate. Between 2010 (when LGI1 and CASPR2 were identified as the main antigens within the VGKC) and 2019, in our Centre (Paediatric Neurology and Neurophysiology Unit, University Hospital of Padua, Italy) the ratio between the number of children with LGI1 and/or CASPR2 autoimmunity compared to that of children with anti-NMDAR encephalitis has been 1:11.

5. Limitations

Our literature review is strongly affected by the retrospective nature of the work and by the very low number of patients, limiting the possibility of drawing definite conclusions. Moreover, length of follow-up was considerably heterogeneous in the three subgroups of LGI1-positive, CASPR2-positive and double-positive patients, hampering definite comparisons between these three subgroups especially regarding follow-up.

6. Conclusions

Despite these limitations, we report the youngest case of Morvan syndrome described to date, and we contribute to the definition of the clinical features of LGI1 and CASPR2 autoimmunity in paediatric age with the first systematic literature review. Our review discloses antibody-specific clinical features in children, in particular suggesting a trend towards predominantly CNS syndromes both in LGI1-positive and in CASPR2-positive patients, and confirms higher representation of predominantly PNS syndromes in double-positive patients (Gadoth et al., 2017). Most frequent syndromes were encephalitis in LGI1-positive and isolated epilepsy in CASPR2-positive children, while syndromes with predominant peripheral symptoms were most frequent in double-positive children. With the limitations imposed by the low number of cases, differences to published adult cohorts included: absence of faciobrachial dystonic seizures and hyponatremia in patients with LGI1-positive encephalitis; slightly higher proportion of isolated epilepsy syndromes in CASPR2-positive patients; absence of tumour in the whole cohort. These may represent age-specific features of LGI1 and CASPR2 autoimmunity in children, although studies in larger cohorts are warranted to verify these observations.

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Appendix A. Supplementary data

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