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LETTER TO THE EDITORS

Pediatric LGI1 and CASPR2 autoimmunity associated with COVID 19: Morvan syndrome

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Dear Sirs,

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) most commonly affects the respiratory system, autoimmune neurological presentations have also been reported [1, 2]. More recently Burr et al. have reported a pediatric patient with SARS-CoV-2-associated anti-NMDAR encephalitis [1]. Although anti-NMDAR encephalitis is one of the most common types of autoimmune encephalitis (AIE) leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein 2 (CASPR2)-associated autoimmunity is rare in children. LGI1 and CASPR2 are the main antigens within the voltage-gated potassium channel-complex (VGKC). LGI1 and CASPR2 autoimmunity is associated with limbic encephalitis, isolated epilepsy, Morvan syndrome and neuromyotonia [3]. Morvan syndrome is characterized by neuromyotonia, dysautonomia, insomnia and neuropsychiatric symptoms [3, 4]. Here we present the pediatric patient with SARS-CoV-2-associated Morvan syndrome initially present with Guillain–Barre syndrome.

A previously healthy 3-year-old girl has admitted to an outside hospital for a history of sleep dysregulation and irritability followed by lower extremities weakness with difficulty in walking for 2 months ago. Her first examination had revealed tachycardia, arterial hypertension, ataxia and abolished deep tendon reflexes of the lower extremities. She had family history of coronavirus disease 2019 (COVID-19) 4 weeks before her symptoms developed. She was tested for screening of COVID-19. SARS-CoV-2 Real-Time Reverse Transcriptase (rRT)-PCR was detected negative on nasopharyngeal swab. SARS-CoV-2 IgG antibodies (ab) from serum were positive. Initial blood chemistry has only revealed mild hyponatremia. CSF analysis demonstrated albuminocytologic dissociation. GBS has been presumed and intravenous immunoglobulin (IVIG) 2 g/kg was administered. Patient received antihypertensive treatment with three medications (metoprolol, enalapril, and prazosin), which showed limited benefit for control of elevated blood pressure. Four weeks following IVIG administration she was still agitated and had no recovery of weakness. Furthermore, she developed hyperhidrosis and pruritus and severe hypertension persisted despite the triple antihypertensive medication.

Patient refeered to our hospital one month after IVIG administration. She had ataxia, sleep dysregulation, nocturnal restlessness, episodes of crying, irritability, hyperhidrosis, tachycardia, and severe arterial hypertension. SARS-CoV-2 IgG and IgM-ab from serum were positive. Blood chemistry showed; mild hyponatremia with 133 mmol/L and increased serum levels of free thyroxine (fT4). Repeated CSF analysis demonstrated albuminocytologic dissociation (Table1). Extended microbiology and oncology screening on blood, bone marrow, and CSF was unremarkable. MRI of the brain with and without contrast, abdominal ultrasound, renal doppler ultrasound, abdominal CT angiography, chest CT, and chest X-Ray were normal. Spine MRI revealed diffuse thickening and enhancement of cauda equina nerve roots. Electroencephalography showed diffuse slowing of the background activity. EMG could not performed. Antineural antibody screening revealed LGI1 (serum titer 1:80) and CASPR2-ab (serum titer 1:160), done by a commercial cell-based assay (Euroimmun, Lubeck, Germany) with a modified protocol. CSF analysis for CASPR2 and LGI1-ab were negative. Ten days after admission to our hospital repeated serum LGI1 and CASPR2-ab remained positive (1/80 and

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Table 1 Summary of laboratory tests at 3 time points

	Time 1: 1–10 D prior to IVIG	Time 2: 30th D following IVIG	Time 3*: 40th D following IVIG	Reference Range
Spinal fluid analysis				
White blood cell count	2		0	0–5
Glucose (mg/dL)			62	40–70
Protein (mg/dL)	**118**		**61.8**	15–45
Albumin (mg/dL)	**73.6**		**55.1**	5–25
IgG (mg/L)	**274**		**75**	3–30
IgG index	**1.7**		0.52	< 0.7
Oligoclonal bands (OCBs)			No OCBs present	
HSV 1, HSV 2 PCR			Negative	
HHV 6,7,8 PCR			Negative	
Enterovirus PCR			Negative	
EBV, CMV, VZV PCR			Negative	
Blood tests				
Anti-AMPA1/AMPA2		Negative	Negative	
Anti-NMDA		Negative	Negative	
Anti GABA- B		Negative	Negative	
Anti-CASPR2		**Positive (1/160)**	**Positive (1/320)**	
Anti-LGI1		**Positive (1/80)**	**Positive (1/80)**	
Anti-Yo, Anti-Hu, Anti-Ri, Anti-Ma2 Anti-CV2		Negative	Negative	
SARS-CoV-2 (rRT)-PCR	Negative	Negative		
SARS-CoV-2 IgG	**Positive**	**Positive**	**Positive**	
SARS-Cov-2 IgM		**Positive**	Negative	
fT4 (pmol/L)		**28.4**		11–22.5
TSH (mIU/L)		2.2		0.54–4.53
Anti-TPO Ab (IU/ml)		18.2		0–34
Complement component 3 (mg/dL)		151.6		70–180
Complement component 4 (mg/dL)		25.5		10–40
ENA**		Negative		
C reactive protein (mg/L)		0.3	0.6	0–5

*One day prior to IV methylprednisolone treatment

**ENA Anti-Ro Ab, Anti-La Ab, Anti-jo-1 Ab, Anti-ScL70 Ab, Anti Sm Ab, Anti-RNP Ab

Abnormal test results are written in bold

1/320, respectively). We diagnosed combination of GBS and Morvan syndrome based on the clinical phenotype and laboratory findings. IV methylprednisolone (30 mg/kg/day) was administered for 5 days and followed by oral prednisolone treatment. Over the following week, sleep dysregulation, nocturnal restlessness, episodes of crying, hyperhidrosis, pruritus and ataxia gradually resolved. Four weeks after IV methylprednisolone administration requirement of antihypertensive medication was reduced and tachycardia was improved. Moreover serum LGI1 and CASPR2-ab, which was repeated for the third time, were detected negative 3 weeks after IV methylprednisolone administration.

Morvan syndrome is a rare autoimmune disorder predominantly affects elderly men with the male to female ratio 19:1 in adult patients [5]. Unique feature of our patient is the female gender. To our knowledge 14 paediartic cases with Morvan syndrome and available antibody results were published and 5 cases were female [3, 4, 6–9]. According to the cases reported so far, the male predominance of Morvan syndrome in children is not as pronounced as in adults and this might possibly represent an age-dependent feature of the syndrome [3].

Serum studies of eight patients with Morvan syndrome have revealed increased serum levels of free thyroxine (5/8), cortisol (2/8), renin (2/8), prolactin (1/8), adrenalin/noradrenalin (3/8), isolated low triiodothyronine (1/8), and hyponatremia (1/8) [4]. Although hyponatremia has been infrequently reported in paediatric cases, was mildly

present in our patient. Lee et. al have reported the different expressions of VGKC in hormone secreting neuronal nuclei within the hypothalamus in rats [10]. They have suggested this molecular diversity of VGKC may provide regulatory mechanisms in controlling endocrine and autonomic systems [10]. This report might explain the abnormalities of different hormonal axes in patients with Morvan syndrome [4, 10]. In our case, serum levels of sodium and fT4 were detected in normal range, 138 mmol/L and 19.3 pmol/L, respectively, 2 weeks after IV methylprednisolone administration.

In pediatric cases, CASPR2-ab-associated GBS has been reported previously [11]. The initial presentation of our patient has also suggested GBS. However, she had marked clinical deterioration despite IVIG administration and later developed clinical and laboratory features compatible with Morvan syndrome. In 2016, Lotan et al. have reported a 61-year-old man who had the combination of GBS-like and classic Morvan syndrome symptoms associated with the sole presence of LGI1-ab [12]. Our patient's clinical presentation was similar to their case. To our knowledge, this is the first pediatric case of confirmed Morvan syndrome presenting initially with GBS and this report broadens the clinical spectrum of LGI1 and CASPR2 autoimmunity.

Paraneoplastic association has been made with thymoma in adult patients with Morvan syndrome. Consistent with previously reported pediatric cases our patient had no thymoma which we ruled out with radiologic investigations. Moreover there also may be possible infectious triggers of the disease [13]. Several pediatric case reports have revealed the association between SARS-CoV-2 infection and the development of autoimmunity [1, 2, 14]. In our case, SARS-CoV-2 IgG and IgM-ab were positive and suggesting that SARS-Cov-2 infection may triggered the CASPR2 and LGI1 autoimmunity.

In conclusion, we defined the relationship between combination of GBS and Morvan syndrome, which is the first report in children, and SARS-Cov-2 infection. Previously reported autoimmune neurologic manifestations in children with SARS-Cov-2 strengthens our theory.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Conflicts of interest This study has been carried out in accordence with the Declaration of Helsinki.

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