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An Unusual but Treatable Cause of Autistic Regression

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Abstract

We report the case of a seven year old male child who presented with regression of cognitive function and loss of speech over a 12 month period. Physical neurological examination was normal with no KF ring. Differential diagnoses considered were Wilson's disease, autoimmune encephalitis and SSPE. CSF analysis was normal. EEG was non-contributory. Serum ceruloplasmin was within normal limits. Serum autoimmune panel had tested positive for CASPR2. Child was treated with pulse methylprednisolone followed by oral steroids. Child's cognitive function and speech have improved to a great extent.

Keywords: Autoimmune • Anti CASPR2 • Autistic regression • Neuromyotonia

Introduction

Autoimmune encephalitis is commonly reported in children and adults presenting with acute or subacute cognitive decline or new onset seizures in a previously normal child. It has a wide clinical spectrum and delineation of specific autoantibodies is important for deciding on the duration of treatment and prognostication. It is reported as young as in a 9 month old infant to as old as in an 80 year old adult. Anti-VGKC antibodies are rarely reported in children and are associated with neuromyotonia and carcinomas. Here we report the case of a 7 year old male child with VGKC associated autoimmune encephalitis.

Case Report

A 7 year old boy presented with the complaints of loss of speech and cognitive decline since one year. He also had sleep disturbances and aggressive behaviour in the form of injuring the care takers. His motor milestones were appropriate but he had an expressive language delay wherein he started to speak 5-10 meaningful words by 4 years of age and phrases by 7 years. He is first born to non-consanguineously married couple and had no significant perinatal events. He was partially immunized for age and had not taken Measles vaccine. There is no significant family history of neurological disorders. On examination he was alert with poor eye contact and no social interaction. Central nervous system examination was normal. Ophthalmological examination showed no evidence of KF ring and fundus examination was normal. Neuropsychological evaluation showed moderate level of deficits in social functioning, MILD level of autistic spectrum symptoms and MILD level of deficits in intellectual functioning.

The clinical differential diagnoses considered were Landau Kleffner syndrome, Wilson`s disease, Subacute Sclerosing Pan Encephalitis (SSPE) and Autoimmune encephalitis.

Electroencephalogram showed bursts of high amplitude slow and sharp waves occurring at intervals of 2-6 seconds (Figure 1). In view of these bursts of high amplitude sharp waves SSPE was considered and benzodiazepenes provocation was done. These bursts did not have a periodic pattern after benzodiazepine administration. Neuroimaging (MRI Brain) was normal. Lumbar puncture was done and CSF analysis revealed total count -0 cells/cu.mm, nil RBC'S, sugar -57mg/dl against blood sugar-120 mg/dl, protein 17 mg/dl, Serum and CSF anti measles IgG antibody was negative. Serum ceruloplasmin was normal -24 mg/dl. Serum autoimmune encephalitis panel was performed and tested positive for CASPR2 (Contactin - associated protein 2/VGKC associated) (Figure 2) and negative for NMDA, AMPA-1 and AMPA-2. As CASPR2 antibodies are associated with neuromyotonia, a nerve conduction study and Electromyography were performed that revealed a normal pattern and Whole body Positron Emission tomography (PET) to look for malignancies was normal. He was pulsed with intravenous methylprednisolone for 3 days followed by oral steroids at 1mg/kg/day and risperidone to control aggressive behaviour. After 4 weeks of starting steroids there is a remarkable improvement in speech (10-20 meaningful words) and well-regulated sleep.

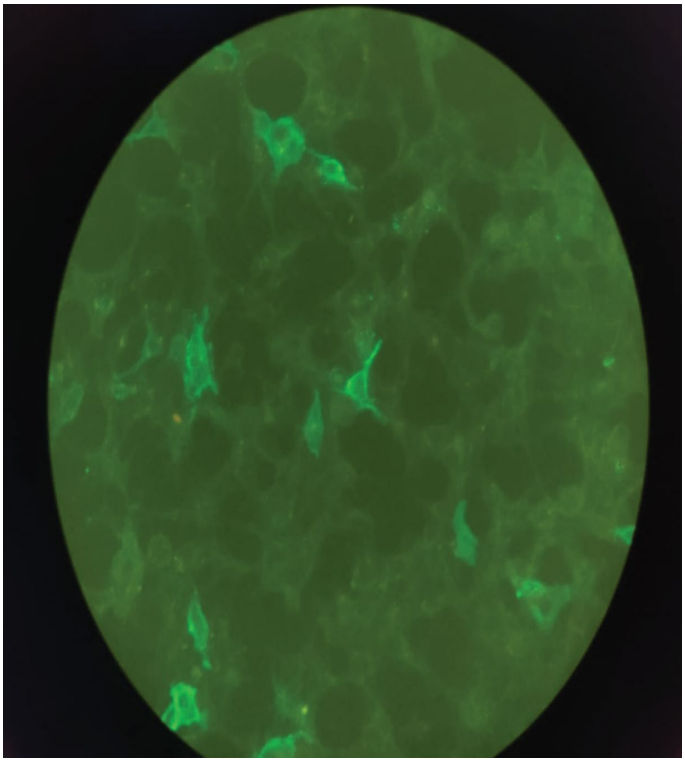

Figure 1. Contactin 2 (CASPR2) protein detected in serum sample.

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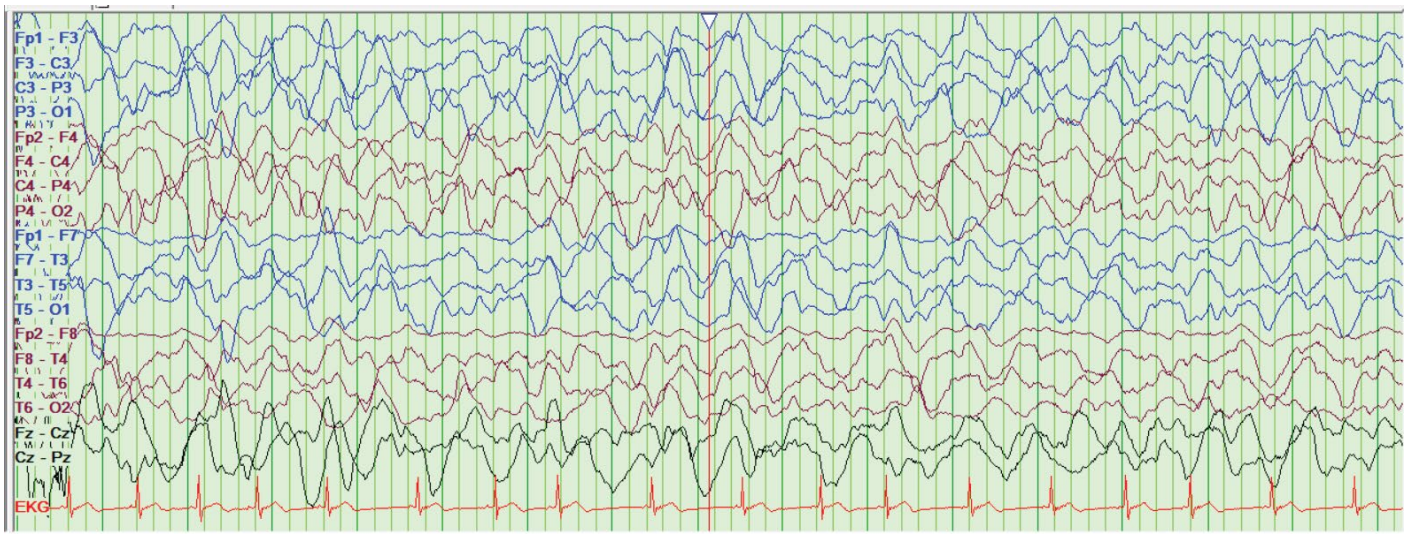

Figure 2. EEG showing high amplitude delta slowing at 15 uV sensitivity.

Discussion

Autoimmune encephalitis (AE) is one of the most common causes of noninfectious encephalitis. AE has a wide variety of clinical manifestations including seizures, movement disorders, autonomic disturbances, behavioral and psychiatric symptoms. Anti CASPr 2 related encephalitis is rare in childhood. LGI1 and Caspr2 antibodies were identified only in one child in a series of 39 children with VGKC complex antibodies mean age of onset of clinical symptoms is 70 years [1].

Patients with anti-LGI1 encephalitis or anti-Caspr2 encephalitis generally show a less severe clinical manifestation and faster recovery than patients with anti-NMDAR encephalitis, which may reflect the limited ability of IgG4 [2]. Hippocampal atrophy, reversible basal ganglia and amygdala abnormalities are being reported. These occur due to complement activation and cytotoxic T-cell-mediated neuronal injury.

CASPR2 is a cellular adhesion molecule (CAM) which is a member of neurexin family. It regulates axonal domains around the nodes of Ranvier. CASPR2 is a transmembrane protein with its C-terminal portion interacting with protein 4.1B-an ankyrin protein that is said to link the juxtaparanodal and paranodal adhesion complexes to the axonal cytoskeleton. Since it is expressed in both central and peripheral nervous system some patients also feature with peripheral nerve hyperexcitability [3].

VGKC-complex antibodies are nonspecific biomarkers for inflammation and its detection in paediatric population mandates to screen them for peripheral neuropathy, neuromyotonia and also to look for paraneoplastic association with mediastinal and lung malignancies. Anti VGKC encephalitis associated with neuromyotonia and cardiac arrythmias is termed as Morvan's syndrome. Our patient did not have neuromyotonia/ paraneoplastic association. The youngest case of Morvan syndrome is that of a 12 month old female child [4].

Anti CASPR-2 related encephalitis when presented as new onset seizures responded well to anti epileptics and may not require immunotherapy. A few of them however required long term immunomodulation with rituximab, mycophenolate mofetil and plasma exchange. The antibody titres of CASPR 2 are reported to become negative after 3 to 4 weeks following methylprednisolone administration, while in some cases they remain persistently elevated despite symptomatic relief [4]. On the other hand there have been cases of dual antibody positivity in serum (anti CASPR and Anti GAD) which have an unremitting clinical course with refractory seizures and unresponsiveness to immunotherapy [2].

Several cases have had COVID viral infection in the past as the trigger for autoimmunity and another uncommon presentation was Guillian-Barre syndrome that failed to respond to Intravenous immunoglobulin. However they respond well to steroids and plasma exchange [5].

Our child however responded well to steroids and behavioural modification therapy without a need for further immunomodulation. He is under regular follow up with us since the past 3 months.

Conclusion

In a child presenting with autistic regression it's worthwhile to investigate for a treatable cause like autoimmune encephalitis. Anti CASPR 2 encephalitis is rarely reported in pediatric population. More extensive data are required for tailoring of immunotherapy based on the type of autoantibodies in serum /CSF in pediatric population.

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