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GRIN1– Related neurodevelopmental disorder–Autism with Epilepsy – A case report

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Introduction

GRIN1-related neurodevelopmental disorders are a group of rare paediatric encephalopathies,with estimated prevalence of 1:5000 births [(1)]. Genetic variation in the GRIN1 gene have been associated with a wide range of neurologic and neuropsychiatric disorders .GRIN1 (Glutamate Receptor Inotropic, NMDA 1) is the name of the gene that is affected..GRIN1 -related disorders, the so-called grinpathies, is caused by mutations affecting *GRIN* genes (mostly *GRIN1, GRIN2A* and *GRIN2B* genes), which encode for the GluN subunit of the *N*-Methyl D-Aspartate (NMDA) of glutamate receptors[(2)]. NMDARs play critical roles in normal brain function, such as neural development, synaptic plasticity, learning, memory, and motor function [(3)].Phenotypes associated with de novo GRIN1 pathogenic variants include severe early onset psychomotor delay in all reported patients and epilepsy in up to 70% of these patients [(4)]. Mutations of the NMDAR subunits are associated with a different neurodevelopmental phenotypes, including intellectual disability (ID),epilepsy, and Autism spectrum disorders (ASD), and psychiatric diseases. [(5)] Other common manifestations are muscular hypotonia, movement disorders, spasticity, feeding difficulties and behaviour issues. A subset of individuals shows a malformation of cortical development consisting of extensive and diffuse bilateral polymicrogyria. [(6)]

The symptoms and severity of the disorder vary widely. There are no typical clinical signs and symptoms of a *GRIN1*-related disorder that enable a diagnosis based on clinical features alone. Genetic study is required to diagnose a *GRIN1*-related disorder. Implementation of next-generation sequencing to clinical diagnosis has allowed reporting of a growing number of both neutral and disease-associated *GRIN1* variants [(2)] To date, 72 individuals with *GRIN1*-NDD have been reported, including 64 individuals with de novo heterozygous pathogenic missense variants and eight individuals from four families with biallelic pathogenic missense or truncating variants[(6)]

This case report highlights the importance of GRIN1 mutations in the etiology of isolated cases of early onset encephalopathy, and the valuable role of whole exome sequencing in identifying these mutations.

Keywords: GRIN1 gene; Autism; Epilepsy

Case report

A 5 year old male child presented with history of speech delay, convulsions and inability to sit in one place. He is a first child born out of nonconsanguineous marriage, he is a term baby delivered by LSCS, birth weight was 3.3 kgs, baby cried immediately after birth, breast fed on day 1 of life. There was no family history of developmental delay or seizures in three-

degree pedigree charting. Child had a normal developmental trajectory upto 1 year 4 months of age.

Developmental history : Gross motor milestones - child achieved neck holding at 3 months, sitting by 7 months, standing by 1year, later there was a mild delay in walking, started walking by 1 year 4 months, running by 2 years, presently child can't jump, they feel his movements are bit clumsy. Fine motor milestones - child achieved pincer grasp by one year and by one and half year of age, parents noticed abnormal shaking movements of hand, shaking toys and household items near his ears to hear sounds, banging things to hear sounds, biting and mouthing things following which child didn't achieve much fine motor skills, now child can scribble with pen. Language milestones: child used to follow simple one step commands by one year of age, used to talk in words, he had a vocabulary of around 7 to 10 words and had good name-call response also.

Around 1 month after 1st episode of convulsion parents noticed regression of his language milestones, child stopped talking in words, used only sounds to communicate, stopped responding to commands, stopped responding to name, started engaging in repetitive movements and child seemed to be in his own world gradually. Presently his receptive and expressive language is around 8 -9 months. Child used to play peek a boo and simple ball game by 1 year of age. But by one and half year child started repetitive behaviour and stopped playing meaningfully. Now his play skills are poor with only mouthing and exploratory play. Social milestones are poor with no pointing, no joint attention, no shared joy...

Behaviour history – Sleep is adequate, appetite is good, not toilet trained, no problematic behaviours. Sensory issues: Child prefers to move always, loves banging and shaking toy to make noise, hypersensitive to cooker and mixer sounds, closes his ears for the same. On examination there were no obvious neurological deficits. Child was diagnosed to have Autism and started on speech and occupational therapy from 3 years of age onwards. Currently child is taking speech, occupational therapy and behavioural therapy classes daily since one year. Parents are not noticing much improvement in his speech and overall behaviour. –

Seizure had varied semiology. Seizures started as typically febrile seizure at the age of 1year 4 months, followed by recurrent febrile seizures once in two months ,around total 5 episodes till the age of 2 years10 months which was treated with Clobazam prophylaxis only. Later around 3 years of age parents noticed recurrent sudden loss of tone for <20 seconds, following which child used to get up and walk. These episodes occuredonce in 20 days around 3-4 episodes in 3 months, EEG was abnormal and diagnosed as Absence seizures and started on carbamzepine after which symptoms subsided. At the age of 4 years 4 months again child had two episodes of unprovoked generalized tonic seizures lasting for <1 min with transient loss of consiousness. Repeat EEG was abnormal so Sodium Valproate was added, carbamazepine was tapered and stopped. Around 4 years 11 months parents noticed jerky movements 2-3 times a day and diagnosed to have myoclonic epilepsy and topiramate was added. But intensity of jerks increased. So clobazam was added. But myoclonic jerks persisted and hence leviteracetam was added to Sodium Valproate and topiramate and clobazam were tapered and stopped. Presently child is on Sodium Valproate and leviteracetam and symptoms are under control.

Investigations showed the following findings. EEG showed multifocal and generalized interictal epileptiform discharges(myoclonic jerk noted during EEG), **MRI** brain was normal. Clinical exome : revealed a heterozygous missense variation in exon 19 of the GRIN1 gene (chr9: g.137163846G>T GRCh38 format;

c.2594G>T) that results in the amino acid substitution of Leucine for Arginine at codon 865 (p. Arg865Leu) was detected in the indexpatient. Arg865Leu is reported as pathogenic mutant as per ACMG criteria PM1, PM2, PM5, PP2, PP5 (Clinvar database reference 598966). Another pathogenic variant at same site Arg865Cys has also been described (Clinvar database reference 521354)

Neurodevelopmental assessments showed the following. Based on observation on the Autism Diagnostic Observation schedule module 1, Pranav obtained a total score of 25 which met the ADOS 2 classification of autism and the level of symptoms being high, Mullens scale of early learning showed overall T score on the early learning composite is interpreted as very low functioning, child had associated sensory issues

Discussion

GRIN1-neurodevelopmental disorder (*GRIN1*-NDD) should be considered in individuals with Mild-to-profound developmental delay or intellectual disability and any of the following symptoms in infancy or childhood which includes epilepsy, Autism spectrum disorder, Microcephaly, Cortical visual impairment, hypotonia or spasticity, dystonic, dyskinetic, or choreiform movement disorder[6] De novo mutations in the GRIN1 gene have been recently reported as the molecular cause of a broad-spectrum early-onset neurodevelopmental delay. In this study, we report one patient who presented with early onset seizure and developmental delay and autism due to a *de novo* pathogenic variant in the *GRIN1* gene. Here we have a five-year-old boy with normal development till 1.4 years had seizures on and off many times till now, initially GTCS but now myoclonic seizures which required trial of multiple antiepileptics associated with regression of acquired speech and features of Autism. Whole-exome sequencing identified a novel p. Met641Leu de novo variant in the GRIN1 gene as the cause of the phenotype. Child also had abnormal EEG- multifocal and generalized interictal epileptiform discharges.

We reviewed literature available on the topic. Tim A. Benke, et al reported patients with *GRIN1*-related neurodevelopmental disorder showing multiple deficits, including ID, epilepsy, hypotonia, movement disorders. All affected individuals evaluated to date show variable levels of ID, 65% had epilepsy, hypotonia (66%), movement disorders (48%), cortical visual impairment (CVI, 34%), oculogyric crises (11%), features of autism spectrum disorders, or stereotypic movement disorder (32%), sleep problem (15%), and self-harm behaviour (7%). The onset of seizure ranges from birth to 11 years of age, and two thirds demonstrated resistance to conventional antiseizure treatment. Seizure types include generalized seizures (68%; with multiple semiologies), focal seizures (2%), and epileptic spasms (13%). some individuals showed cortical malformations like extensive bilateral polymicrogyria, ventriculomegaly, reduced thickness of the corpus callosum, basal ganglia dysplasia, and decreased white matter volume. In our case child has autism and seizures of multiple semiologies presently requiring trail of multiple antiepileptics. MRI was normal despite developmental delay and Seizures[7]. Konrad et al, reported 72 individuals with *GRIN1*-NDD, including 64 individuals *denovo* heterozygous pathogenic missense variants and eight individuals from four families with biallelic pathogenic missense or truncating variants. All affected individuals have a variable degree of DD or ID (profound in 17%, severe in 71%, moderate in 7%, mild in 5%). No active speech has been noted in 48% of individuals. Seizures occurred in 65% of individuals. Some affected individuals presented with different seizure types over time. In 27 individuals with seizures, 17 had refractory seizures and 10 were well controlled with standard anti-seizure medication. Signs of autism spectrum disorder were observed in 22%.

Other behavior issues observed were stereotypic movements (32%), self-injurious behavior (7%), and sleep disorder (15%). ([6]). Johannes R. Lemke, et al, study on 23 patients carrying de novo *GRIN1* mutation presented with profound global developmental delay, 71% had hypotonia , spasticity in 29%, dyskinetic movement disorders (61%), Nonspecific stereotypic movements in 33%. 70% had epilepsy with different. Seizure semiology (infantile spasms, tonic and atonic seizures, hypermotor seizures, focal dyscognitive seizures, febrile seizures, generalized seizures, status epilepticus), and the associated EEG pattern (hypsarrhythmia, focal, multifocal and generalized spikes and waves). 31% therapy-resistant epilepsy, 2 patients became seizure-free, 2 patients responded to topiramate, levetiracetam, and clobazam. 8(35%) *GRIN1* patients were diagnosed with ASD or ASD-like features (5). Jin Zhang et al reported 20 patients with 26 pathogenic variants in the *GRIN1* gene. Phenotypes associated with *de novo GRIN1* pathogenic variants include severe early onset psychomotor delay in all reported patients and epilepsies in up to 70% of these patients. [(3).] Fry et al. recently reported *de novo* pathogenic variants in the *GRIN1* gene in 11 patients with extensive bilateral polymicrogyria. Our case here has pathogenic variant GRIN1, with Autism with seizure with movement disorder. Brain MRI is normal in our case[(8)]. ChihiroOhba et al - study on GRIN1 mutations in children with unclassified early onset epileptic encephalopathy, with nonsyndromic intellectual disability and concluded that Clinical features of infantile involuntary movements, seizures, and hand stereotypies, suggesting that GRIN1 mutations cause encephalopathy resulting in seizures and movement disorders[(9)]. Yuchen Xu, et all assessed the effects of a set of FDA-approved NMDAR channel blocker memantine, which significantly improved the patient's seizure burden, with evidence that seizures worsened considerably during transient discontinuation of memantine and concluded that appropriate clinical trials including more *GRIN1* patients are necessary to further establish the safety and efficacy, especially with respect to neurodevelopmental outcomes, for long-term use of memantine and considered as future hope for children with GRIN mutations[(10),]

Conclusion : De novo GRIN1 mutations are being identified more often cause of neurodevelopmental delay with seizure. Our case report suggests that the novel *de novo GRIN1* variant (type variant) is associated with developmental delay, autism and epilepsy. GRIN1-encephalopathy should be suspected in early onset seizures with neurodevelopmental delay. Whole Exome Sequencing (WES) will help in diagnostic testing in suspected cases.

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