JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S6

A case of early-onset epileptic encephalopathy in infant with Autosomal recessive GRIN1 related neurodevelopmental disorder caused by homozygous nonsense variant.

Mohammed Rajeh ALHAYLI[1]; Tarig Yassin Alamery[2]; Attiasaleh Ali Alzahrani[3]; Ahmed Yaseen Mofareh Alamari[4]; Awad Ali Alessi[5]; Fuad Mohammed Alkudaysi[6]; Ali Abdulaziz Mohammed Alghanmi[7]; Turki Mohammed Alhasani[8]; Hassan Ibrahim Yahya Alnashri[9].

1. Consultant of Pediatric and NICU, Department of Pediatric, South Qunfudah Hospital, Kingdom of Saudi Arabia.
2. Consultant of Pediatric Gastroenterology,Department of Pediatric, South Qunfudah Hospital, Kingdom of Saudi Arabia.
3. Consultant of NICU, Department of Pediatric, Maternity and Children Hospital Makkah, Kingdom of Saudi Arabia.
4. Public Health Specialist, King Fahad Hospital Jeddah, Kingdom of Saudi Arabia.
5. General physician, Alshargia PHC, Makkah Health Cluster, Kingdom of Saudi Arabia.
6. Pediatric Resident, Department of Pediatric, South Qunfudah Hospital, Kingdom of Saudi Arabia.
7. Pediatric Resident, Department of Pediatric, Khamis Mushayt Maternity and Children Hospital, Kingdom of Saudi Arabia.
8. Pediatric Resident, Department of Pediatric, Khamis Mushayt Maternity and Children Hospital, Kingdom of Saudi Arabia.
9. Pediatric Resident, Department of Pediatric, Khamis Mushayt Maternity and Children Hospital, Kingdom of Saudi Arabia

Abstract
Glutamate receptor, ionotropic,NMDA-1(GRIN1)geneencodesGluN1 subunit of NMDA receptor. Pathogenic variants cause an autosomal dominant or recessive neurodevelopmental disorder (ADorARGRIN1-NDD).Although the reported cases to date less than 100 individuals, most of them ADGRIN1-NDD, only nine were described as ARGRIN1-NDD. Here were porta homozygous variantin GRIN1in a4- month-old boy with early infantile epilepticence phalopathy. As suggested by literature, individuals carrying homozygous nonsense variants exhibit more severe phenotype, which could be explained by complete splicing disruptionofGRNI1 transcription.
Keywords: GRIN1;developmental disorder; epilepsy; nonsense variant; NMDA.

Introduction

NMDA receptors are ion channel receptors that respond to glycine and glutamate agonists acting as calcium permeable channels [1]. These receptors are heteromeric proteins that are composed of two molecules of GluN1, with either two molecules of Gln N2 or one each of Gln N2 and Gln N3 [2,3]. These subunits are the products of three related gene groups: Each subclass contains GRIN1, GRIN2a-d and GRIN3a-b [3]. The NMDA receptors are involved in ongoing synaptic plasticity process which is fundamental to learning and memory [4].

Glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 1 (GRIN1) (OMIM 138249) is a gene which gives rise to the GluN1 subunit of the NMDA receptor. GRIN1 is mapped to the chromosome 9q34.3 [5] and extends on for approximately 31kb and contains 21 exons [6].

Pathogenic variants in GRIN1 have been described to cause GRIN1-related neurodevelopmental disorders (GRIN1-NDD, MIM #614254 and #617820): heterozygous de novo and homozygous biallelic. These disorders are expressed through developmental delay, intellectual disability, epilepsy, muscular hypotonia, movement disorders, spasticity, feeding problems and behavioral disorder [7].

Currently, the number of causative cases has been confirmed at 72 instances of GRIN1-NDD. While the majority of the cases are indeed the autosomal dominant form of GRIN1-NDD due to heterozygous mutations; only nine individuals are described to have autosomal recessive GRIN1-NDD (AR GRIN1-NDD) resulting from homozygous variants. This population encompass three of consanguineous origin with a homozygous nonsense variant [8], five subjects belonging to three families affected by homozygous truncating mutations [8,9,10], and one case recently described as carrying a homozygous D94N GRIN1 null variant [11].

Disruption of synaptoplastic NMDA receptors remains implicated in a broad spectrum of neurological and psychiatric diseases because of its significant role in developing higher nervous system. Deleterious mutations in GRIN1 and other associated gene products interfere with the receptor function and obstruct the proper flow of excitatory neurotransmission investment and neurodevelopmen Value.
Homozygous GRIN1 mutations described to date depict a variant range of disease severity outcomes. These include but are not limited to severe integrated developmental disorder, multliple disabilities like Global Developmental Delay, Profound Intellectual Disability disorder and Complex Motor disorder inclusive of Spasticity, Hypotonia Dystonia and others.

For the identification of common clinical features, the variability in the epileptic seizure manifestation of patients suffering from GRIN1-NDD adds to the clinical heterogeneity of this disorder. While in some cases children develop intractable epilepsy right after the birth, in other cases symptoms are not even manifested through seizures. The details of the molecular bases of these differences remain to be unveiled, but could be related to effects of specific mutations on the receptors' conformation and activity. For instance, nonsense or truncating variants may cause loss of function, while missense variants may cause changes of receptor kinetics or ion channel properties. There is clearly a role for additional future studies to refine these genotype-phenotype associations and define their relevance to specific treatments.

Conservative management options are still the primary treatment for patients with GRIN1-NDD and recent treatment measures aimed at improving seizures control, physical exercises, and nutritional support. Managing seizures in these patients is rather a challenge because AEDs' effectiveness in these cases is poor, and seizures frequently remain uncontrolled. Thus, there are approaches to developing new pharmacological interventions, such as the modulation of NMDA receptors, that are currently tested in animal models. These modulators are usually expected to alleviate the consequences of a disease by improving agonist binding or stabilizing channel gating. Nevertheless, they have not yet been extensively tried in clinical practice.

From a genetic counseling point of view it becomes important to determine whether MUT of the GRIN1 gene is inherited in an autosomal dominant or recessive manner in affected families. AR GRIN 1-NDD, even though rare, has a high statistical propensity of recurrence in congregate cultures that practice consanguinity. So, for couples with diseases of a familiar nature, or who are carriers of pathogenic genes, preimplantation genetic testing and prenatal diagnostics can be valuable choices.

New technology of next generation sequencing has enhanced the diagnostic rates of these Neurodevelopmental disorders including GRIN1-NDD. WES and WGS have helped to uncover new variants and the overall spectrum of mutation of GRIN1. These technologies also allow functional studies to determine the virulence potential of newly characterized variants and to lay the foundation for personalized medicine in the context of functional studies.

Subsequent studies should concentrate on creating animal models and cellular systems which might hold functional consequences of GRIN1 mutations. Such models can give information concerning the molecular mechanisms affected by NMDA receptor malfunction and possible therapeutic approaches. Furthermore, cohort and follow up studies with clarification of the course of GRIN1-NDD would provide better insight into the progression of the disease and the effectiveness of new management strategies which may crop up in future.

Collectively, therefore, GRIN1-NDD is a group of disorders which is complex and phenotypically diverse; their impact to individuals and families is great. Future prospects of research in the genetics underlying these diseases, the development of disease-modifying treatments and better approaches to clinical care of these patients remain critical for reducing the morbidity and mortality of diseases of the nervous system.

HerewereportacaseofARGRIN1-NDDcausedbyhomozygousnonsensevariant, ininfantwithearlyinfantileepilepticencephalopathy,presentedmainlywithintractable seizure and abnormal movement.

Results Casereport

Patient Overview:

- **Age**: 4 months
- **Sex**: Male
- **Gestation**: 31 weeks (preterm)
- **Birth Weight**: 1.5 kg

- **Parental Consanguinity**: Yes
- **Delivery**: Cesarean section (due to breech presentation)
- **Antenatal History**: Normal

Clinical Presentation:

The patient presented with generalized tonic-clonic seizures within 30 minutes of birth, along with feeding difficulties and apnea necessitating pulmonary support for five days. Neurological examination revealed microcephaly (head circumference < 3rd percentile), increased muscle tone in all limbs, and jerky movements upon stimulation. Developmentally, the patient exhibited severe global delay, with no milestones achieved, including social smiling, babbling, or eye contact by the time of the last assessment.

Investigations:

1. **Electroencephalogram (EEG):**
   - The EEG demonstrated a burst suppression pattern indicative of epileptic myoclonic encephalopathy.
2. **Magnetic Resonance Imaging (MRI):**
   - Brain imaging was unremarkable, apart from microcephaly.
3. **Genetic Testing:**
   - Exome sequencing identified a homozygous nonsense GRIN1 variant (c.1877C>A; p.(Ser626*)), classified as likely pathogenic according to ACMG/AMP/ClinGen SVI guidelines.
4. **Biochemical and Metabolic Testing:**
   - Results were within normal limits.
5. **Karyotype:**
   - Normal.

Management: The patient demonstrated refractory seizures, unresponsive to multiple antiepileptic drugs (clonazepam, phenobarbital, levetiracetam, phenytoin, and pyridoxine). Partial seizure control was achieved with clobazam. Supportive care included the use of proton pump inhibitors and nasogastric tube feeding. The patient remains under regular outpatient follow-up.

Results in Context: Table 1 provides a detailed comparison of the clinical, genetic, and developmental characteristics of this patient with previously reported cases of autosomal recessive GRIN1-related neurodevelopmental disorder (GRIN1-NDD).

Table 1. Comparison of Clinical Features in GRIN1-NDD Cases

Report	This Report	Blakes et al. (2022)	Rossi et al. (2017)	Rossi et al. (2017)	Lamke et al. (2016)	Lamke et al. (2016)	Lamke et al. (2016)	Lamke et al. (2016)	Lamke et al. (2016)	Bosch et al. (2016)
Parental Consanguinity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA
Variant	c.1877C>A	c.394-1G>C	c.679G>C	c.679G>C	c.742C>T	c.649C>T	c.1666C>T	c.1666C>T	c.1666C>T	c.679G>C
Consequence	p.(Ser626*)	NA	p.(Asp227His)	p.(Asp227His)	p.(Arg217Trp)	p.(Arg217Trp)	p.(Gln556*)	p.(Gln556*)	p.(Gln556*)	p.(Asp248His)
Zygosity	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Age at Last Assessment	4 months	12 months	5 years	3 years	13 years	12 years	5 months (RIP)	12 days (RIP)	8 days (RIP)	6 years
Sex	Male	Male	Female	Male	Male	Male	Male	Female	Female	Female
Seizure Onset	Day 1	Day 2	No seizures	No seizures	No seizures	No seizures	Day 1	Day 1	Day 1	No seizures
Seizure Types	Myoclonic, Tonic-clonic	Myoclonic jerks, diaphragmatic jerks, lip smacking, limb clonus	NA	NA	NA	NA	Myoclonic, clonic with desaturation, refractory to treatment	Clonic, refractory to treatment	Clonic, refractory to treatment	NA
EEG	(1	(1 week)	Normal	Not	(6	(10	Burst	Burst	Burst	NA

(Age)	month) Burst suppression	Myoclonic encephalopathy		done	months) Spikes during sleep; (13 years) Unstructured, slow activity	months) Diffuse spikes and waves during sleep; (11 years) Left temporal spikes	suppression	suppression	suppression	
MRI (Age)	(4 months) Normal	(1 month) Normal	(18 months) Mild cerebral atrophy, thin corpus callosum	(1 year) Normal	(6 months) Normal	(10 months) Normal	(1 month) Possible punctiform hemorrhage in thalami	Not done	Microcephalic, delayed myelination, delayed sulci formation	White matter abnormalities
Behavior	Encephalopathic	Initially encephalopathic, lacks interaction, turns to sound	Autistic, stereotypic midline movements	Autistic, stereotypic midline movements	Autistic, agitation, self-injury, laughing outbursts, stereotypic midline movements	Autistic, stereotypic midline movements, agitation	Encephalopathic	NA	NA	Staring at lights
Development	Severe global developmental delay	Severe global developmental delay, no smile, lacks head control, no palmar grasp	Severe intellectual disability, no language, non-ambulant	Severe intellectual disability, no language, non-ambulant	Severe intellectual disability and developmental delay, absent speech	Severe intellectual disability and developmental delay, absent speech, non-ambulant	Profound global developmental delay	No development	No development	Delayed (further information unavailable)
Neurological Findings	Intractable seizures, increased tone in all limbs, jerky movements on stimulation	Central hypotonia, limb contractures, oromotor dysfunction	Hypotonia	Hypotonia	Axial hypotonia, tetraspastic, distal amyotrophy, dystonic movements	Axial hypotonia, tetraspastic	Hypotonia at birth, later hypertonic	Hypotonia at birth, then hypertonia, microcephaly, opisthotonic posturing	Continuous seizures	Central hypotonia

Other Features	Microcephaly	Autonomic cardiac dysfunction, unsafe swallow, reflux	Frontal bossing, mild midface hypoplasia	Frontal bossing, left transverse palmar crease	Constipation	Constipation, gynecomastia, macroglossia, sleep disorder	Hyperlaxity of thumbs, sandal gap toes	NA	NA	Facial dysmorphism, recurrent upper airway infections, feeding problems

This case underscores the severe clinical phenotype associated with GRIN1-related neurodevelopmental disorder, including early-onset, refractory seizures and profound developmental delay. Despite normal neuroimaging, genetic analysis identified a pathogenic GRIN1 variant, highlighting the importance of molecular diagnostics in early-onset epileptic encephalopathy. The findings align with previously reported cases while demonstrating variability in clinical features, including seizure types and neurological outcomes.

Discussion

ARGRIN1-NDD caused by homozygous variant sextremely rare with only nine reported cases, in contrast with heterozygous variants which account the vast majorityoftheGRIN1-NDDcases[8-11].

Reported cases of ARGRIN1-NDD show a clinical picture of severe global developmental delay, severe intellectual disability, neurological disorders[11]. Our proband exhibits an early infantile epileptic encephalopathy phenotype. This consistent with previous reports on nonsense homozygous variants which show more sever neurologic phenotypes[11]. There is only one family with 3 individuals has been reported to carry nonsense homozygous variants, all did not survive bey ondinfancy[8]. This could be explained by complete splicing disruption of GRNI1transcription[11]. One case reported recently withAR GRIN1-NDD caused by a novel homozygous splice acceptor variant, and the patient presented with severe neurologic phenotype during early infancy, but he survives after 12 months of age. There port suggests in complete disruption of GRIN1 transcription that all owing some residual expression of completeGRIN1 transcripts, resulting in a truncate dbutviable transcript could be the cause that patient survives till this age [11].

Conclusions

In conclusion, we suggest that ARGRIN1-NDD causedbyhomozygous nonsense variants can be associated with more severe clinical phenotype and death.

References

[1] Johnson,J.W.,&Ascher,P.(1987).GlycinepotentiatestheNMDAresponsein cultured mouse brain neurons. Nature, 325(6104), 529-531.

[2] Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K.K.,...&Dingledine,R.(2010).Glutamatereceptorionchannels:structure,regulation,and function. Pharmacological reviews, 62(3), 405-496. DOI: https://doi.org/10.1124/pr.109.002451

[3] Beesley,S.,&Kumar,S.S.(2023).ThetN-methyl-d-aspartatereceptor:Making thecaseford-Serinetobeconsidereditsinverseco-agonist.Neuropharmacology, 109654. doi: https://doi.org/10.1016/j.neuropharm.2023.109654

[4] Paoletti,P.,Bellone,C.,&Zhou,Q.(2013).NMDAreceptorsubunitdiversity:impactonreceptorproperties, synapticplasticityanddisease.NatureReviews Neuroscience, 14(6), 383-400. DOI: 10.1038/nrn3504

[5] Brett,P.M.,BOURDELLES,B.L.,See,C.G.,Whiting,P.J.,Attwood,J.,Woodward, K.,...&Gurling,H.M.D.(1994).GenomiccloningandlocalizationbyFISHandlinkageanalysisofthehumangeneencodingtheprimarysubunitNMDAR1(GRIN1) of the NMDA receptor channel.Annals of human genetics,58(2), 95-100. doi: https://doi.org/10.1111/j.1469-1809.1994.tb01879.x

[6] Zimmer, M., Fink, T. M., Franke, Y., Lichter, P., & Spiess, J. (1995). Cloning andstructureofthegeneencodingthehumanN-methyl-D-aspartatereceptor(NMDAR1).Gene,159(2), 219-223. doi: https://doi.org/10.1016/0378-1119(95)00044-7

[7] Platzer, K., & Lemke, J. R. (2021). GRIN1-related neurodevelopmental disorder. https://www.ncbi.nlm.nih.gov/books/NBK542807/#grin1-ndd.REF.stan_k.2018.71

[8] Lemke, J. R., Geider, K., Helbig, K. L., Heyne, H. O., Schütz, H., Hentschel, J., ... & Syrbe,S.(2016). Delineating the GRIN1phenotypicspectrum:adistinctgenetic NMDA receptor encephalopathy. Neurology, 86(23),2171-2178. doi:

https://doi.org/10.1212%2FWNL.0000000000002740

[9] Rossi, M., Chatron, N., Labalme, A., Ville, D., Carneiro, M., Edery, P., ... &Lesca, G. (2017).NovelhomozygousmissensevariantofGRIN1intwosibswithintellectual disabilityandautisticfeatureswithoutepilepsy.EuropeanJournalofHuman Genetics, 25(3), 376-380. doi: https://doi.org/10.1038%2Fejhg.2016.163

[10] Bosch,D.G.,Boonstra,F.N.,deLeeuw,N.,Pfundt,R.,Nillesen,W.M.,deLigt,J.,..& deVries,B.(2016). Novelgeneticcausesforcerebralvisualimpairment.European Journal of Human Genetics,24(5), 660-665. doi: https://doi.org/10.1038/ejhg.2015.186

[11] Blakes, A. J., English, J., Banka, S., & Basu, H. (2022). A homozygous GRIN1 null variantcausesamoreseverephenotypeofearlyinfantileepilepticencephalopathy.American Journal of Medical Genetics Part A,188(2), 595-599. doi: https://doi.org/10.1002/ajmg.a.62528