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Case Report

Novel homozygous *GLDC* variant causing late-onset glycine encephalopathy: A case report and updated review of the literature

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ABSTRACT

Glycine encephalopathy (MIM #605899) is an autosomal recessive inborn error of metabolism caused by pathogenic variants in three genes *GLDC*, *AMT*, *GCSH* encoding glycine cleavage enzyme system. We report an 8-year-old boy with late-onset glycine encephalopathy who harbors a novel homozygous *GLDC* likely pathogenic variant c.707G > A p.(Arg236Gln). Polyhydramnios was noted at fetal ultrasound. He displayed global developmental delay, craniofacial dysmorphism, convulsions. Our report expands the phenotypic and genetic spectrum of late-onset nonketotic hyperglycinemia.

1. Introduction

Deleterious pathogenic variants in the glycine cleavage system P protein (GCSP) encoded by *GLDC* gene (MIM *238300) have been reported to cause autosomal recessive glycine encephalopathy (MIM #605899) characterized by early-onset neonatal hypotonia, progressive lethargy, poor feeding, seizures, developmental delays, hyperactivity with or without choreatic movements. Of note, approximately 20% of patients with glycine encephalopathy harbor *GLDC* gene deletion. Brain MRI often shows thin and shortened corpus callosum, hydrocephalus, cerebral atrophy, ventricular dilatation, hypomyelination [1]. Most of patients with glycine encephalopathy have an uneventful pregnancy with normal delivery (Supplementary Table S1) [2–29]. Here, we document an 8-year-old-boy with late-onset nonketotic hyperglycinemia (NKH) in whom WES revealed a novel homozygous *GLDC* likely pathogenic variant c.707G > A p.(Arg236Gln). Second trimester fetal ultrasound showed polyhydramnios. To the best of our knowledge, this is the first report of late-onset glycine encephalopathy with abnormal prenatal findings.

2. Clinical report and results

This 8-year-old boy presented for the genetic consultation because of global developmental delay and epilepsy. Fetal ultrasound at 26 weeks of gestation showed polyhydramnios and dilated umbilical veins (Fig. 1A, right image). He was born prematurely by caesarean section at 26 + 1 weeks of gestation to first-cousin consanguineous parents and presented with umbilical hernia, intraventricular hemorrhage at birth. His birth weight, length and occipitofrontal circumference were respectively 1060 g (> 50th percentile), 37.5 cm (> 50th percentile) and 25.5 cm (>50th percentile) with Apgar score of 8/7. Examination of the placenta demonstrated giant chorioangioma (Fig. 1A, left image). He displayed respiratory distress at 2-month-old, right hydrocele at 5-month-old. Recurrent respiratory infections, peripheral hypertonia and axial hypotonia were also noted. Brain MRI showed Dandy-Walker malformation (hydrocephalus, cerebellar hypoplasia and retrocerebellar cyst), bilateral posterior periventricular leukomalacia (Fig. 1B). He experienced his first epilepsy at the age of 2-year-6-month-old which was controlled by treatment of valproate sodium (200 mg x2 per day) and levetiracetam (300 mg x2 per day). Electroencephalogram (EEG) showed multifocal spikes. He underwent endoscopic third

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ventriculocisternostomy for the treatment of hydrocephalus.

On last clinical assessment at the age of 8-year-4-month-old, his weight, height, and head circumference were 26 kg (50-75th percentile), 130 cm (50-75th percentile) and 53.5 cm (>50th percentile). He had global developmental delay, began to walk at 32 months and spoke his first word at 24 months. He also had severe learning disability, dyslexia, and dysgraphia. Deep tendon reflexes revealed hyperreflexia of the upper limbs as well as hypertonia of the lower extremities. Dysmorphic features included long face, high forehead, high arched eyebrows, bilateral ptosis, strabismus, low-set ears, long philtrum, thin upper lip, upturned corners of the mouth and bilateral camptodactyly (Fig. 1C). Ataxic gait and bilateral valgus were also noticed. 180 K array Comparative Genomic Hybridization (array-CGH) showed no chromosomal imbalances. Targeted next-generation sequencing of 95 genes involved in epilepsy revealed a normal result. Trio WES identified a novel homozygous missense likely pathogenic variant in *GLDC* gene c.707G > A p.(Arg236Gln) (Fig. 1D) (PM2, PM3, PM5, PP3, PP4 ACMG criteria, and 4 likely functional affect according to ABC functional "A" grading of ESHG). No *GLDC* intragenic deletion were detected (Supplementary Table S2). The parents were heterozygous. This variant allele was absent in 13,006 chromosomes from Exome Server Variant (https://evs.gs.washington.edu/EVS/) and found at a frequency of heterozygotes of 1193×10^{-5} in 251,476 control chromosomes (3 heterozygous individuals/251,476 subjects) in the gnomAD databases (https://gnomad.broadinstitute.org/). Moreover, the variant *GLDC* c.707G > A p.(Arg236Gln) is predicted to be deleterious by suite of bioinformatics prediction analysis programs. The substitution of a charged amino acid arginine with a polar amino acid glutamine at 236th position results in the decrease of the P protein stability (Supplementary Table S3). The Arg^{236} is highly conserved during species and predicted to be intolerant to changes by MetaDome (https://stuart.radboudumc.nl/metadome/) and Phyre^2 (http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index) (Fig. 2). Molecular modelling of Arg236Gln based on the human glycine decarboxylase structure showing a complete reorganization of the non-covalent interactions of the region (Supplemental Fig. S1).

Metabolic investigation showed the plasma glycine level increased to 1029 μmol/L (reference value 113–397 μmol/L) and elevated urine glycine of 4280 mmol/mol creatinine (reference value <250 mmol/mol creatinine).

After 12 h and 30 min of fasting, blood redox status showed a normal result [lactic acid 1.2 mmol/L (reference value 0.5–1.8 mmol/L), pyruvic acid 0.10 mmol/L (reference value 0.05–0.12 mmol/L), lactate/pyruvate ratio 12 mmol/mmol (reference value 7–16), beta-hydroxybutyric acid (B) 0.02 mmol/L (reference value <0.22-), total ketone body 0.05 mmol/L (reference value 0.02–0.40 mmol/L),

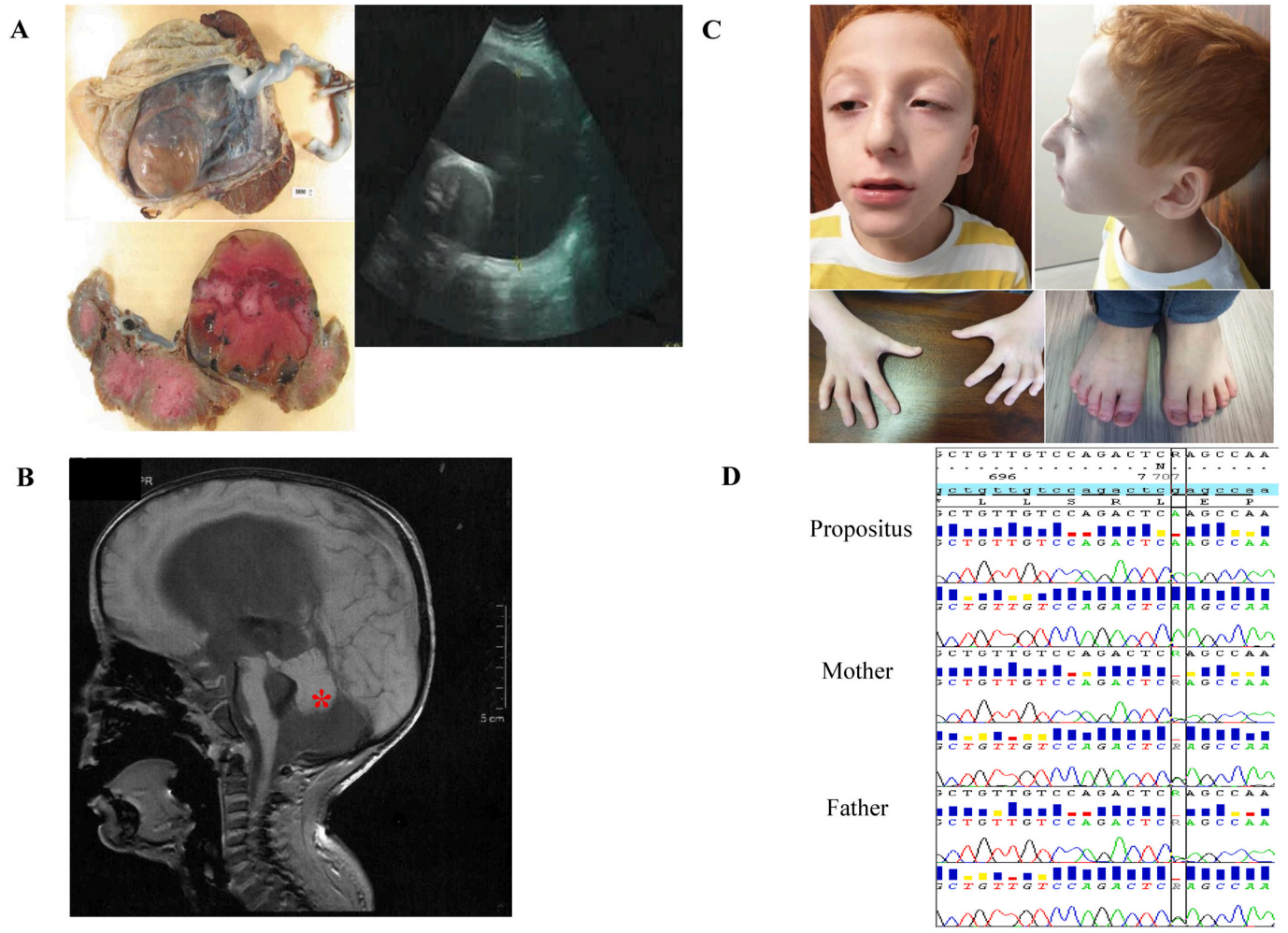

Fig. 1. A. Placental examination showing moderate villous hydrops associated with large chorioangioma (left picture) and prenatal ultrasound showing polyhydramnios at 26 weeks of gestation (right picture). B. Brain MRI showing Dandy-Walker malformation with cerebellar hypoplasia (red asterisk). C. Front and lateral views of the patient showing facial dysmorphism including elongated face with high forehead, high arched eyebrows, ptosis and strabismus, low-set ears, long philtrum, thin upper lip, upturned corner of the mouth, and bilateral camptodactyly. D. Sanger sequencing identified a homozygous novel *GLDC* variant c.707G > A p.(Arg236Gln) in the propositus. The parents were heterozygous.

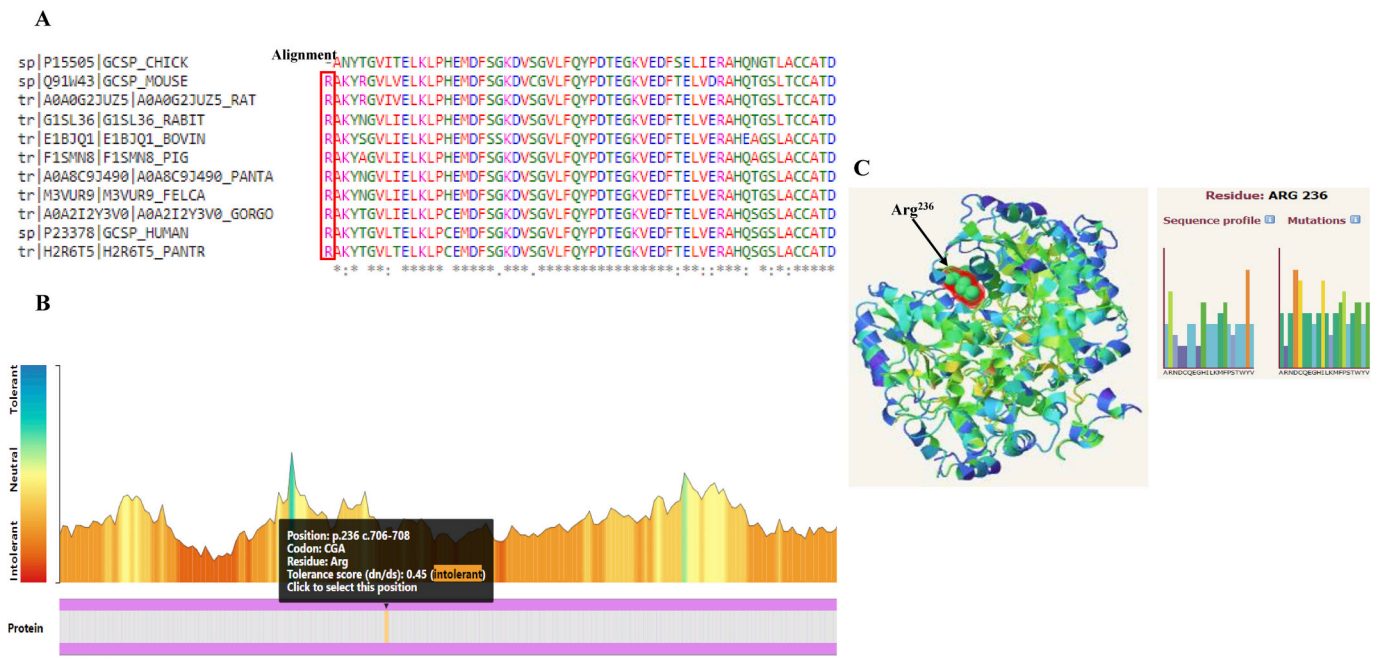

Fig. 2. A. ClustalW showing the Arg^{236} is highly conserved among orthologs. B. Graphic representation of the mutation tolerance score of the affected Arg^{236} of the glycine cleavage system P protein obtained by MetaDome web server indicating that missense variants occurring at this position is intolerant. C. Phyre^2 showing 3D glycine cleavage system P protein structure, the replacement of the charged Arg^{236} by polar glutamine amino acid is moderately intolerant and represent with green color (Arg^{236} is surrounded by red color, mutational sensitivity score = 4).

acetoacetic acid (A) 0.03 mmol/L (reference value 0.00–0.15 mmol/L), (B/A) ratio 0.67 mmol/mmol (reference value >1), free fatty acid 0.66 mmol/L (reference value 0.20–1.20 mmol/L)]. Repeated plasma glycine showed hyperglycinemia of 1414 μmol/L confirming the nonketotic hyperglycinemia without ketone bodies. Indeed, the analysis of amino acids in the plasma, along with the molecular analysis result and clinical manifestation, proved the diagnosis of nonketotic hyperglycinemia.

3. Discussion

We report the new case of late-onset nonketotic hyperglycinemia with a confirmed novel homozygous missense variant in the *GLDC* gene. The variant c.707G > A p.(Arg236Gln) has never been reported in the public databases (homozygous *GLDC* variant c.707G > A p.(Arg236Gln) was absent in 264,482 control chromosomes). It is predicted to result from a substitution of a charged arginine amino acid from a polar glutamine amino acid at the 236th position of the glycine cleavage system P protein. The Arg^{236} is highly conserved among orthologs, and its substitution is also predicted to be "intolerant" or "probably damaging" by MetaDome and Phyre^2 and decrease the stability of the P protein by a suite of bioinformatics analysis prediction (Fig. 2, Supplementary Table S2). We performed a PUBMED search of all studies including keywords "*GLDC* gene, glycine encephalopathy, nonketotic hyperglycinemia" from 1964 to 2022. Eligible publications had to include at least age of disease-onset, symptomatology, initial biochemical data [Cerebrospinal fluid (CSF) glycine, plasma glycine and CSF/plasma ratio], EEG, brain imaging and molecular genetic result. Studies missing clinical phenotype and/or genetic information were all excluded.

Having reviewed the medical literature, only seventeen *GLDC*-mutated patients with prenatal record have been documented so far and all of them have uneventful pregnancy with normal delivery [2–12]. Of interest, this is the first case-report of nonketotic hyperglycinemia with prenatal findings. The propositus was born at 26 + 1 weeks of gestation due to polyhydramnios and giant chorioangioma.

Of note, he was referred to the clinical genetics department because of his seizure and global developmental delay without metabolic investigation. He exhibited unusual, infrequent phenotype of nonketotic hyperglycinemia with the presence of antenatal polyhydramnios and chorioangioma, facial dysmorphism and Dandy-Walker malformation which were rarely observed in late-onset nonketotic hyperglycemic patient. Consequently, the diagnosis of nonketotic hyperglycinemia was not established in the absence of metabolic investigation. Trio whole-exome sequencing was performed to unravel the molecular pathogenesis of epilepsy associated with Dandy-Walker malformation in the propositus with the identification of a novel homozygous *GLDC* missense variant. In addition, he displayed particular prenatal phenotype which seems to be incompatible with attenuated nonketotic hyperglycinemia leading to suspect the presence of other variants in genes implicated in folic acid metabolism. However, neither pathogenic variants nor copy-number variations were detected in *MTHFR*, *MTR*, *MTRR* genes.

Indeed, the presence of non-specific phenotype and difficulty in obtaining CSF samples could hamper the clinical diagnosis of late-onset nonketotic hyperglycinemia and delay the therapeutic strategy [3]. The residual glycine cleavage system enzyme activity caused by different genetic variants can lead to distinct clinical presentation.

The majority of *GLDC*-mutated patients have no dysmorphic features or unavailable data of craniofacial dysmorphism. Hitherto, only two reported *GLDC*-mutated patients display minor dysmorphic features including low-set ears and micrognathia [13]. *GLDC* disease-causing pathogenic variants account for approximately 80% NKH cases. 85% patients had severe neonatal NKH and up to 30% patients died during the neonatal period making difficult to assess, continue regular follow-up and evaluate the craniofacial dysmorphism, particularly in neonates with minor craniofacial changes [1,11,13,22,23,29]. So, the detailed data of facial dysmorphic features are commonly not available in most cases (Supplementary Table S1).

Moreover, brain imaging usually showed cerebral volume decrease or brain atrophy, ventricular dilatation, white matter abnormalities, hypogenesis of the corpus callosum, short and thin corpus callosum in severe NKH, diffusion restriction in the posterior limb of the internal capsule, focal cerebral hemorrhage, and diffuse hypomyelination. Cerebellar atrophy was reported only in one glycine encephalopathy patient (Supplementary Table S1) [1,30]. Our patient is the second case

presenting with Dandy-Walker malformation [31]. Our study shows that apneic episode/respiratory distress is one of the most common clinical features which was observed in 37% patients with glycine encephalopathy (Supplementary Table S1).

In conclusion, this is the first report of late-onset nonketotic hyperglycinemia presenting abnormal prenatal ultrasound findings with polyhydramnios, giant chorioangioma leading to the preterm labor. We also highlight the importance of WES in the diagnosis of inherited metabolic disorders, especially in the case of unspecific phenotype and difficulty in obtaining CSF samples for metabolic investigation. Our observations confirm the clinical heterogeneity of nonketotic hyperglycinemia and expand the phenotypic and molecular spectrum of *GLDC*-related glycine encephalopathy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2023.100959.

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Code availability statement

Not applicable.

Authors' contribution

M.T.H designed the study and wrote the manuscript. J-M.D.S.G and E.L. performed the molecular analysis. A.P. performed the prenatal ultrasound. D·D-L.C and H·B performed patient's follow-up and critically revised the manuscript.

Ethical approval statement

This work is not clinical research and considered as routine clinical care.

Consent for publication

Written informed consent of this case report was obtained from the patient's parents who have given their permission to publish the patients' photographs.

Declaration of Competing Interest

The authors declared no conflicts of interest.

Data availability

The data was submitted in LOVD databases (Leiden Open Databases): Individual #00424557: https://databases.lovd.nl/shared/individuals/00424557.

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