RESEARCH

Spectrum of neuro-developmental disorders in children with congenital hyperinsulinism due to activating mutations in *GLUD1*

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Abstract

Background: Hyperinsulinism/hyperammonemia (HI/HA) syndrome is the second most common type of congenital hyperinsulinism caused by an activating *GLUD1* mutation.
Objective: The aim of this study was to determine the clinical profile and long-term neurological outcomes in children with HI/HA syndrome.
Method: This study is a retrospective review of patients with *GLUD1* mutation, treated at two centers in the UK and Russia, over a 15-year period. Different risk factors for neuro-developmental disorders were analysed by Mann–Whitney U test and Fisher's exact *P* test.
Results: We identified 25 cases with *GLUD1* mutations (12 males). Median age of presentation was 7 months (12 h–18 months). Hypoglycaemic seizures were the presenting feature in 24 (96%) cases. Twenty four cases responded to diazoxide and protein restriction whilst one patient underwent partial pancreatectomy. In total, 13 cases (52%) developed neurodevelopmental manifestations. Epilepsy (n = 9/25, 36%), learning difficulties (n = 8/25, 32%) and speech delay (n = 8/25, 32%) were the most common neurological manifestation. Median age of presentation for epilepsy was 12 months with generalised tonic-clonic seizures being the most common (n = 4/9, 44.4%) followed by absence seizures (n = 3/9, 33.3%). Early age of presentation (P = 0.02), diazoxide dose (P = 0.04) and a mutation in exon 11 or 12 (P = 0.01) were associated with neurological disorder.
Conclusion: HI/HA syndrome is associated with wide spectrum of neurological disorders. These neurological manifestations were more frequent in cases with mutations affecting the GTP-binding site of *GLUD1* in our cohort.

Key Words

- hyperinsulinism/hyperammonemia
- HI/HA syndrome
- *GLUD1*
- neurodevelopmental disorders
- epilepsy

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Introduction

Hyperinsulinism/hyperammonemia (HI/HA) syndrome is the second most common cause of congenital hyperinsulinism (CHI) after *ABCC8/KCNJ11* mutations. It is caused due to an activating mutation in the *GLUD1* gene, which is located on chromosome 10q23.3 (contains 13 exons) and encodes the intra-mitochondrial matrix enzyme glutamate dehydrogenase (GDH). Approximately 70% of these children have *de novo* mutation and 30% present with autosomal dominant inheritance (1, 2).

GDH is highly expressed in pancreatic β-cells, liver, kidney and brain, where it plays an important role in the metabolism of amino acids and ammonia (3). In pancreatic β-cells, it catalyses the oxidative deamination of glutamate to alpha-ketoglutarate and ammonia. Alpha-ketoglutarate enters the tricarboxylic acid cycle (Krebs cycle), leading to increase in ATP production, which finally results in insulin exocytosis (4). GDH is allosterically activated by leucine and inhibited by guanosine-5'-triphosphate (GTP) (5, 6). Activated mutations in the *GLUD1* gene lead to loss of this allosteric inhibition by GTP, which in turn increases leucine-induced glutamate oxidation to alpha-ketoglutarate, resulting in hyperinsulinemic hypoglycaemia (7). This leucine-sensitive hypoglycaemia clinically presents as postprandial hypoglycaemia (following protein-rich food) and HA, which are two classical and persistent features of this condition.

Clinically, children with HI/HA syndrome present in late infancy, with fasting and/or postprandial (after protein-rich meal) hypoglycaemia. An elevated ammonia level, which is a striking feature, seems to be consistent even without hypoglycaemia. However, unlike the HA of urea cycle defect, these children do not have symptoms of raised ammonia (8).

Patients with HI/HA syndrome are prone to develop different neurodevelopmental disorders including epilepsy (9). Delayed presentation, recurrent hypoglycaemia, raised ammonia level and/or increased GDH activity in the brain are some of the proposed explanations for this brain damage; however, the exact pathogenesis is unclear (10).

In this study, we aimed to assess the frequency of different neurodevelopmental disorders including epilepsy in children with HI/HA syndrome due to a *GLUD1* activating mutation. We further explored the significance of different risk factors that can lead to the development of neurological disorders in these children.

Materials and methods

We retrospectively analysed all cases of HI/HA syndrome due to an activating mutation in the *GLUD1* gene, presenting in paediatric endocrine centres in London and Moscow over a period of 15 years (2003–2018). Local research and development ethical approval for retrospective data collection was obtained as per institutional requirements of contributing centres (Great Ormond Street Hospital, London, UK, and Endocrinology Research Centre, Moscow, Russia (protocol No 18 from 11.10.17)).

The clinical spectrum of these children including gestational age, birth weight, presence of neonatal newborn complications, age of presentation, presenting complaints, family history, neurological manifestation and treatment response was reviewed. HI was confirmed in all cases biochemically on provocation tests suggestive of detectable insulin (>2.0 mIU/L) and c-peptide (>100 pmol/L) at the time of hypoglycaemia (<3.0 mmol/L) and suppressed fatty acids and ketone bodies.

Gene testing for Russian patients included *GCG, GLUD1, WFS1, HNF1A, GCK, INS, HNF1B, ABCC8, HNF4A, RFX6, PTF1A, NEUROD1, AKT2, ZFP57, INSR, EIF2AK3, PPARG, PAX4, PDX1, GLIS3, KCNJ11, SLC16A1, FOXP3, BLK, CEL, KLF11, GCGR* and *HADH.* For UK patients, Sanger sequencing of *GLUD1* gene was performed as a first-line test as all the patients presented with strong clinical suspicion of HI/HA syndrome.

Neurological assessment of mental status, motor and sensory function, cranial nerves and reflexes by an experienced neurologist and detailed neurodevelopmental assessment by a community paediatrician as per local protocol were performed in every case. Of the 25 genetically confirmed cases of HI/HA, electroencephalography (EEG) was performed in 14/25 cases and MRI brain was performed in 12/25 cases. A spectrum of neurological disorders was assessed using percentages. Suggested risk factors for neurodevelopmental disorder and epilepsy included gender, birth weight, gestational age, prematurity, age of presentation, ammonia level at presentation, glucose infusion requirement at presentation, dose of diazoxide, history of asphyxia and mutation site. Children with and without neurodevelopmental disorders and those with and without epilepsy were divided into separate groups. Non-binary data were analysed with the help of Mann–Whitney U test and binary data by Fisher's exact *P* test with *P* value < 0.05 considered as significant.

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Results

We included 25 cases of HI/HA cases due to an activating *GLUD1* mutation (13 females and 12 males). The median current age of the children enrolled is 8 years. Most of the children were born at term with normal birth weight (Table 1). The vast majority presented with hypoglycaemic seizures during the first year of life (median age of presentation is 7 months); presentation after the first year of life occurred only in three cases.

More than half of the patients experience neurodevelopmental disorders (56%) with epilepsy being the most common (36%), followed by learning difficulties, speech delay, motor delay, abnormal movement and vision problem (Fig. 1). A total of 14 cases had an EEG, with 6/14 (43%) showing abnormality. MRI brain was performed in 12 cases with 6/12 showing abnormal findings (50%).

Median age of epilepsy onset was 12 months (from 4 weeks to 8 years). Among 13 children with epilepsy, 3 cases presented with generalised tonic-clonic (GTC) seizures, 2 cases with absence seizures, 1 child with a combination of GTC and absence seizures and in 3 cases the type of seizures were not specified. Monotherapy (sodium valproate, lamotrigine) was effective in 6/13 cases (Table 2).

Neurodevelopmental disorders were associated with early age of presentation ($P=0.02$), higher diazoxide requirement ($P=0.04$) and a mutation in exon 11 or 12 ($P=0.01$). No relevant risk factors for epilepsy were identified (Table 3).

Almost all patients (24/25) responded very well to diazoxide (median dose 7 mg/kg/day) along with dietary advice (to have mixed meals with carbs and protein and avoiding pure protein-rich meal). One patient underwent partial pancreatectomy due to uncontrolled hypoglycaemia while on octreotide (diazoxide was not used in that index case as it was not available at that time).

Ammonia level was found to be raised in almost all the cases where data were available (17/25) both at normoglycaemia and hypoglycaemia (data were unavailable in 8/25 children but was reported to be raised on referral).

Discussion

HI/HA syndrome is a distinctive form of diazoxide responsive CHI, which is characterised by fasting/postprandial recurrent hypoglycaemia, asymptomatic HA and association with neurological manifestations including epilepsy (11, 12, 13, 14, 15). Children with HI/HA syndrome often present after 4–6 months of life and usually have normal birth weight (7, 16, 17). This was also observed in our study where the median age of presentation was 7 months and the median birth weight was 3654 g. One of the striking findings in our cohort was that 8 of the 25 cases (32%) presented within the neonatal period. This is a higher frequency of neonatal presentation of HI/HA syndrome compared to previously reported studies where it ranges from 15 to 18% (9, 18, 19). Interestingly, all these children with neonatal presentation in our cohort had a mutation within exon 11 or 12. This association was also observed by Su and coworkers (9) who reported three out of four cases of HI/HA syndrome with neonatal presentation having a mutation in exon 11 or 12 of *GLUD1*. This suggests that an activating *GLUD1* mutation within these two exons may result in a more severe phenotype leading to an earlier presentation.

Children with HI/HA syndrome are prone to develop various neurological manifestations including epilepsy (7, 10, 11, 20, 21). Epilepsy has been reported in children with HI/HA syndrome with frequency ranging from 46 to 64% (18, 19, 21, 22). In our study, epilepsy was the most reported neurological disorder with an overall frequency of 32%. Similar to our findings, many other studies have suggested GTC seizures and absence seizures, as the most common type of epilepsy associated with HI/HA syndrome (18, 19). Bahi-Buisson and coworkers (18) reported that 79% of HI/HA with epilepsy respond to monotherapy while the remainder of patients required combination therapy. This is comparable to our study where 46% of epilepsy responded well to monotherapy. We did not find an association between epilepsy and suggested risk factors (age of presentation, gender, gestational age, prematurity, birthweight, asphyxia, ammonia level, glucose requirement at presentation, diazoxide dosage and mutation in exon 11 or 12). The limited number of patients could be a limiting factor for revealing statistical significance. Previous studies have suggested an association between *GLUD1* mutations affecting exon 6 or 7 with epilepsy (9, 18, 19).

Learning disabilities, speech delay, motor delay, abnormal movements (tics, dystonia, ataxia, spasticity) and vision problems were other neurological disorders observed in our cohort. Among these, learning disabilities are well reported in previous studies (18, 20, 21, 23). In our series, 32% of patients had learning disabilities, which were frequently associated with epilepsy. An interesting finding in our study was the development of abnormal movements disorder in six cases (24%). Bahi-Buisson and coworkers also reported this finding in 2 out of 22 cases (9%) (18).

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Table 1 Neurodevelopmental disorders in children with HI/HA syndrome.

Case	Exon	Protein change	Nucleotide change	Age of presentation	Gestational age in weeks	Birth weight (grams)	Epilepsy	Learning difficulties	Speech delay	Motor delay	Abnormal movement	Vision problem
01[a]	11	p.(Ser498Leu)	c.1506C>T	4 months	39	3628	Yes	Yes	Yes	Yes	No	No
02[a]	7	p.(His315Tyr)	c.956C>T	7 months	Not known	Not known	No	No	No	No	No	No
03[b]	7	p.(Arg322His)	c.965G>A	8 months	38	1170	No	No	No	No	No	No
04[a]	6	p.(Arg274Cys)	c.820C>T	9 months	Not known	2000	No	No	No	No	No	No
05[b]	11	p.(Ser498Leu)	c.1493C>T	3 days	38	Not known	No	Yes	Yes	Yes	Yes (ataxia)	Yes (central vision)
06[b]	7	p.(Arg318Ile)	c.953G>T	1 year	42	Not known	No	No	No	No	No	No
07[a]	6	p.(Arg274Cys)	c.820C>T	10 months	Not known	3628	No	No	No	No	No	No
08[b]	11	p.(Pro489Leu)	c.1466C>T	4 days	Not known	Not known	No	Yes	No	No	No	No
09[b]	6	p.(Arg274Cys)	c.820C>T	18 months	42	Not known	Yes	No	No	No	Yes (tics)	No
10[b]	11	p.(Ser498Leu)	c.1493C>T	12 hours	40	Not known	Yes	Yes	No	No	No	Yes (bilateral cataract)
11[b]	7	p.(Arg318Lys)	c.953G>A	4 months	40	4960	Yes	Yes	No	No	No	No
12[b]	11	p.(Ser498Leu)	c.1493C>T	12 hours	39	3939	No	No	No	No	No	No
13[c]	6	p.(Arg274Cys)	c.820C>T	13 months	40	3790	No	No	No	No	No	No
14[c]	7	p.(Arg322His)	c.965G>A	4 months	41	4360	No	No	No	No	No	No
15[c]	11	p.(Ser498Leu)	c.1493C>T	9 months	41	3850	Yes	Yes	Yes	Yes	No	No
16[c]	12	p.(Gly499Arg)	c.1495G>A	7 days	36	4200	Yes	No	Yes	Yes	No	No
17[c]	6	p.(Arg274Cys)	c.820C>T	10 months	40	2290	No	No	Yes	No	Yes (ataxia)	No
18[c]	7	p.(Arg322His)	c.965G>A	13 months	40	3700	No	No	No	No	No	No
19[c]	7	p.(Arg322His)	c.965G>A	8 months	40	3840	No	No	No	No	No	No
20[c]	11	p.(Ser498Leu)	c.1493C>T	2 months	38	3680	Yes	Yes	Yes	Yes	Yes (ataxia, dystonia)	No
21[c]	11	p.(Ile497Met)	c.1491A>G	10 months	39	2870	No	No	No	No	No	No
22[c]	12	p.(Gly499Val)	c.1496G>T	15 days	Not known	3000	No	No	No	Yes	No	Yes (optic nerve atrophy)
23[c]	11	p.(Ser498Leu)	c.1493C>T	4 days	38	3020	Yes	Yes	Yes	No	Yes (spasticity)	Yes (myopia, amblyopia)
24[c]	11	p.(Asn463Asp)	c.1387A>G	1 months	40	3580	Yes	No	Yes	Yes	Yes (dystonia)	No
25[c]	11	P.(Ser498Leu)	c.1493C>T	9 months	39	3100	No	No	No	No	No	No

[a]Genetic testing done by others; [b]Genetic testing done by Exeter university; [c]Genetic testing done by Russian team.

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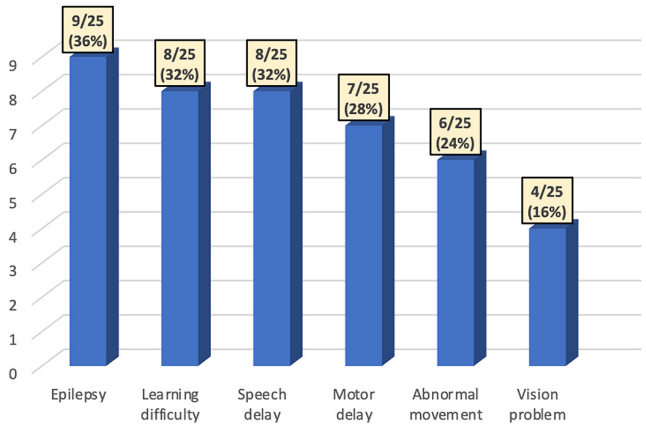

Figure 1
Neurodevelopmental disorders in children with HI/HA syndrome.

The pathophysiology of these neurodevelopmental disorders including epilepsy resulting from an activating *GLUD1* mutation is not well understood and is likely to be complex. Many theories have been proposed including chronic HA, late presentation, recurrent hypoglycaemia and increased GDH activity in the brain. However, none of these can fully explain the underlying mechanism. We tried to improve understanding by evaluating the association of different risk factors with neurodevelopmental disorders and epilepsy in our study. High ammonia level, which should be detrimental to the developing brain, was not associated with neurological manifestation including epilepsy (P=0.62 and P=0.92, respectively). *GLUD1* patients hardly mimic any signs and symptoms of HA (11). Many authors like in our study failed to establish the association between HA and neurodevelopmental disorders in HI/HA syndrome (9, 18). Moreover, lowering blood ammonia with sodium benzoate and N-carbamoyl glutamate led to no improvement (24). Early age of presentation and higher dose of diazoxide were associated with neurological manifestation in our cohort (P=0.02 and P=0.04, respectively). We also observed a statistically significant association between mutations in exon 11 or 12 and neurological disorder, whereas previous studies reported the association of exon 6 or 7 with epilepsy (9, 18, 19) or no association with the location of a mutation at all (11, 18, 21, 25).

This may indicate that children with activating *GLUD1* mutations located within exon 11 or 12 may have severe disease, with increased GDH activity in different body tissues including the brain and pancreas. Overactivity of GDH in the pancreas might explain the reason for severe phenotype of CHI leading to early presentation and higher dose of diazoxide. Similarly, increased activity of GDH in the brain leading to disequilibrium between glutamate and γ-aminobutyric acid could account for higher frequency of neurological disorders (26, 27, 28).

Whilst it is too early to speculate on why mutations in exons 11 and 12 have a more dramatic effect on the neurological system, understanding the role of the exons is important. Exons 6 and 7 encode the NAD-binding domain that forms catalytic cleft. Exons 11 and 12 encode the antenna, a unique allosteric domain. Mutations confined to exons 11 and 12 interfere with GTP and ATP inhibition of GDH, which leads to increased activity of the enzyme (23).

We can also make an assumption that mutations in exon 11 and 12 lead to hypoglycaemia-induced brain damage due to severe pancreatic disease. However, we doubt hypoglycaemic brain damage to be the main reason for neurological manifestation in these children. All patients are well-controlled with no recurrent hypoglycaemia, most of them show normal brain MRI, and those with abnormal MRI findings are not suggestive of hypoglycaemic brain damage. Our cohort presented with GTC and absence seizures in contrast to hypoglycaemia-induced focal epilepsy.

Table 2 Clinical spectrum in HI/HA children with epilepsy.

Case no	Gender	Age of presentation	Seizure type	EEG	MRI	Treatment responded	F/H of epilepsy	Asphyxia, sepsis
1	F	6 months	GTC and absence	Not known	Normal	Lamotrigine, levetiracetam	No	No
9	F	12 months	Absence	Normal	Normal	Lamotrigine	No	No
10	F	2 years	Absence	Not known	Normal	Lamotrigine	No	No
11	M	8 years	GTC	Normal	Normal	Lamotrigine, valproate	Yes	No
15	M	15 months	Not known	Abnormal	Not done	Valproate	No	No
16	F	11 months	GTC	Abnormal	abnormal	Valproate	No	No
20	F	10 months	GTC	Abnormal	Abnormal	Valproate, carbamazepine	No	No
23	M	4 years	Not known	Abnormal	Abnormal	Valproate	No	No
24	M	1 month	Not known	Abnormal	Abnormal	Valproate	No	No

EEG, electroencephalogram; GTC, generalised tonic-clonic;, F/H, family history; F, female; M, male.

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Table 3 Risk factors for neurodevelopmental disorders.

Risk factors	Neurodevelopmental disorders, *P* value	Epilepsy, *P* value
Age of presentation (weeks)	**0.02**	0.16
Gestational age (weeks)	0.77	0.32
Birth weight (gram)	0.96	0.30
Ammonia level	0.62	0.92
Glucose requirement at presentation (mg/kg/min)	0.07	0.54
Diazoxide dosage (mg/kg/day)	**0.04**	0.22
Gender	0.58	0.56
Prematurity	0.68	0.68
Asphyxia	0.09	0.09
Mutation in exon 11 or 12	**0.01**	0.06

In this study, the small number of patients, due to the rarity of the condition, and the absence of some data (ammonia level, MRI results) in several cases have lessened statistical significance. Even in the cases where the association was found, we cannot claim robust results. Another limitation is that this clinical study cannot reveal the underlying cause of the link between mutation site and neurological disorders, and further functional tests are needed. We are also unable to exclude the neurological impact of subclinical hypoglycaemic episodes that could have happened before the clinical presentation of the HI.

Conclusion

Children with HI/HA syndrome due to an activating mutation in the *GLUD1* gene are prone to neurodevelopmental disorders. Epilepsy is the most common, followed by learning difficulties and speech delay. Except well-known risk factors, we revealed that mutations in exon 11 and 12 are more likely to lead to neurodevelopmental disorders.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
Sommayya Aftab: collected data, literature review and wrote manuscript. Diliara Gubaeva: collected data, analysed data; Antonia Dastamani: literature review; Ellada Sotiridou: collected data; Clare Gilbert: collected data; Jayne Houghton: collection of genetic results and analysis; Sarah E Flanagan: collection of genetic results and analysis; Anatoliy Tyulpakov: collection of genetic results and analysis; Maria Melikyan: collected data, analysed data and wrote manuscript; Pratik Shah: conceived the idea, collected data and wrote manuscript; M Melikyan and P Shah: joint last authors.

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