Spectrum of Neuro-developmental Disorders in Children with Congenital Hyperinsulinism due to Activating Mutations in *GLUD1*

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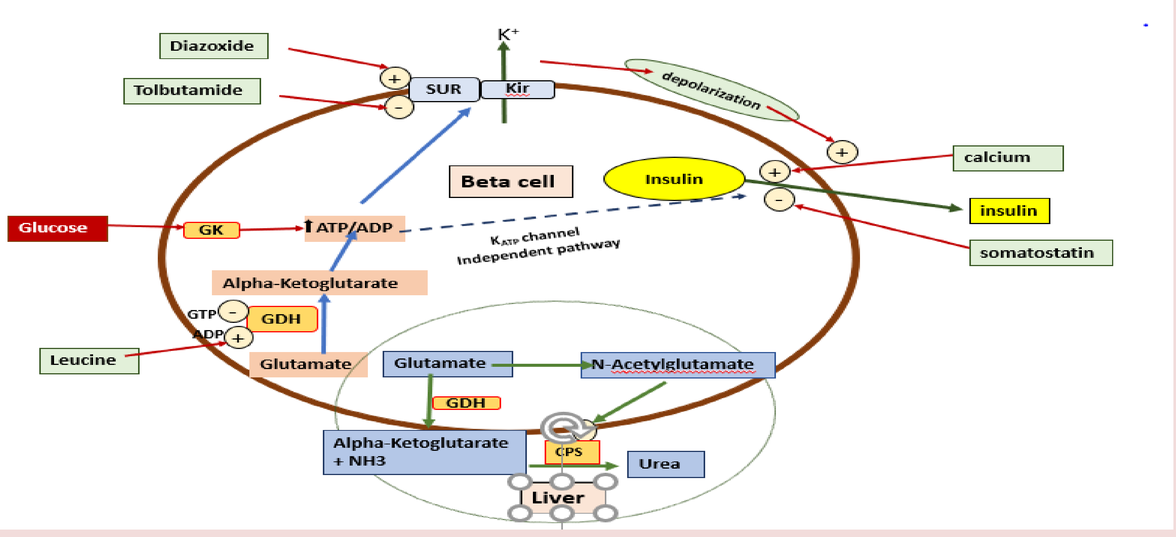
Background

- Hyperinsulinism hyperammonaemia (HI/HA) is the second most common type of congenital hyperinsulinism due to activating mutation in *GLUD1* gene. (Figure 1)
- These children are prone to have neurodevelopmental disorder.
- Pathophysiology of this association is complex and multifactorial like delayed presentation, raised ammonia and increased glutamate dehydrogenase (GDH) activity in brain.

Aim

- To determine the clinical presentation, treatment and risk factors of neuro-developmental disorders in children with HI/HA syndrome due to activating *GLUD1* mutation.

Figure 1- Pathogenesis of hyperinsulinism hyperammonaemia due to activating mutation of *GLUD1*



Methodology

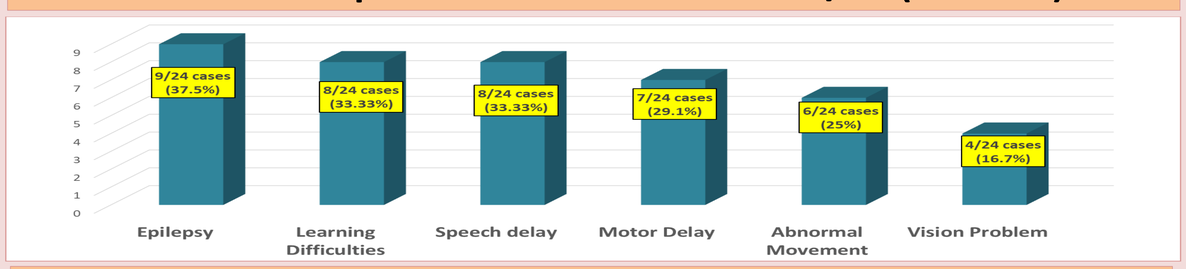
- Retrospective review of patients with *GLUD1* mutation at two specialist centers in the UK and Russia over a 15-year period.
- Statistical analyses included Mann-Whitney U and Fisher P tests to assess the significance of different risk factors for neuro-developmental disorders.

Results

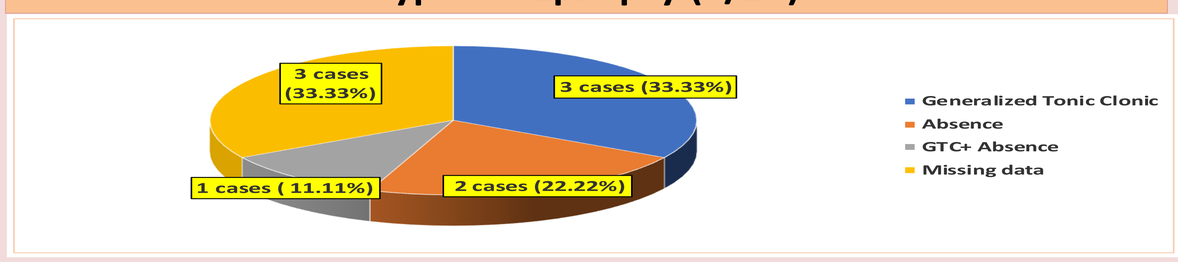
Clinical spectrum of *GLUD 1* Mutation

- Total 24 cases of *GLUD1* mutation (11 males).
- Hypoglycaemia was the presenting complain in 23/24 cases and one presented with unexplained screaming.
- Mean age of presentation was 23.8 weeks (12 hours-72 weeks).
- 23/24 cases responded to diazoxide and 1 case underwent pancreatectomy.
- Neurological manifestation was found in 16/24 cases with epilepsy being the most common (9/24), followed by learning difficulties (8/24) and speech delay (8/24).
- Mean age of presentation of epilepsy was 15.9 months (1month – 8 years)

Neurodevelopmental manifestation 16/24 (66.75 %)



Types of Epilepsy (9/24)



Risk factors assessment for neuro-developmental disorders

Mann-Whitney U test

Non Binary Risk factors	p-value
Age of Presentation (weeks)	0.04
Ammonia Level (umol/l)	0.41
Birth Weight (grams)	0.95
Gestational Age	0.09
GIR (mg/kg/min)	0.09
Diazoxide dose (mg/kg/day)	0.06

Fisher P test

Binary risk factors		Group 1 with neuro-developmental disorders	Group 2 without neuro-developmental disorders	p-value
Mutation in Exons	11 and 12	10	2	0.00061
	6 and 7	03	9	
Gender	Male	6	5	0.64
	Female	7	6	
Prematurity	Yes	1	1	0.70
	No	7	9	
Asphyxia	Yes	3	0	0.10
	No	8	11	
Mode of inheritance	De Novo	7	5	0.06
	Inherited	0	4	

Early age of presentation (p-value 0.04) and mutation in Exon 11 and 12 (p-value 0.0006) were associated with neurodevelopmental disorder

Risk factors assessment for epilepsy

Mann-Whitney U test

Non-Binary risk factors	p-value
Age of Presentation (weeks)	0.19
Ammonia Level (umol/l)	0.92
Birth Weight (grams)	0.37
Gestational Age	0.33
GIR (mg/kg/min)	0.06
Diazoxide dose (mg/kg/day)	0.30

Fisher P test

RISK FACTORS		Group 1 with epilepsy	Group 2 without epilepsy	p – value
Mutation in Exons	11 and 12	7	5	0.04
	6 and 7	02	10	
Gender	Male	4	7	0.60
	Female	5	8	
Prematurity	Yes	0	2	0.35
	No	7	9	
Asphyxia	Yes	2	1	0.29
	No	6	13	

Mutation in Exon 11 and 12 seems to be associated with epilepsy p-value 0.04

Conclusion

- Neuro-developmental disorders were seen in 66.7% of our cohort.
- Epilepsy (37.5%) was the most common neurological disorder followed by learning difficulties (33.3%) and speech delay (33.3%).
- Mutation in exon 11 and 12 seems significant risk factor for neuro-developmental disorder (p=0.0006) and epilepsy (p=0.04).
- Early age of presentation seems to be associated with neurodevelopmental disorders (p=0.04)

References

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2. Su C, Liang X, Li, WJ, Wu D, Liu M, etal. Clinical and Molecular Spectrum of Glutamate Dehydrogenase Gene Defects in 26 Chinese Congenital Hyperinsulinemia Patients. J Diabetes Res 2018 Sep 16;2018:2802540