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

RFC9-005	Sommayya Aftab ¹ *, Diliara Gubaeva ² *, Antonia Dastamani ¹ , Ellada Sotiridou ¹ , C Jayne Houghton ³ , Sarah E. Flanagan ³ , Maria Melikyan ² **, Pratik Shah ¹ **	lare Gilbert ¹ ,	
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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.

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



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.

Methodology

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

Mann-Whitney U test				Fisher P test			Mann-Whitney	n-Whitney U test			Fisher P test				
Non Binary Risk factors Age of Presentation (weeks)	p-value	Binary risk factors		Group 1 with neuro- developmental disorders	Group 2 without neuro- developmental disorders	p-value	Non-Binary risk factors Age of Presentation (weeks)	p-value 0.19	RISK FAC	CTORS	Group 1 with epilepsy	Group 2 without epilepsy	p – value		
Ammonia Level (umol/l)	0.41	Mutation in	11 and 12	10	2	0.00061	Ammonia Loval (umol/l)	0.92	11 and 12 7	5					
		Exons	6 and 7	03	9		Ammonia Level (umol/l)		Mutation in Exons	$\frac{11 \text{ and } 12}{6 \text{ and } 7}$	02	10	- (0.04)		
Birth Weight	0.95	Gender	Male	6	5	0.64			LAOIIS		02	- 10			
(grams)			Female	1	6		Birth Weight (grams)	0.37	Gender	Male	4	/	0.60		
Gestational Age	0.09	Prematurity	res	1	1 0	0.70	Gestational Age	0.33		Female	5	8			
CIP (mg/kg/min)	0.00		Yes	2	0		CIP (mg/kg/min)	0.06	Prematurity	Yes	0	2	0.35		
Gik (ing/kg/min)	0.09	Asphyxia	No	8	11	0.10	Gik (ing/kg/iiiii)	0.00	. rematanty	Νο	7	9			
Diazoxide dose (mg/kg/day)	0.06	Mode of inheritance	De Novo	7	5		Diazoxide dose	0.30	Asphyxia	Yes	2	1	0.29		
	i		Inherited	0	4	0.06	(mg/kg/day)			Νο	6	13			
Early age of presentation (p-value 0.04) and mutation in Exon 11 and 12 (p-value 0.0006) were associated with neurodevelopmental disorder p-v Conclusion										s to be as 0.04	sociated	l with epil	epsy		
 Neuro-dev Epilepsy (3) Mutation Early age of 	velopmenta 37.5%) was in exon 11 of presenta	al disorde the most and 12 se tion seen	rs were commo ems sign ns to be	seen in 66.7% on neurologica nificant risk fa associated w	6 of our coh al disorder actor for ne ith neurode	ort. followe uro-dev evelopm	d by learning diffic velopmental disord nental disorders (page	ulties (ler (p=0 =0.04)	33.3%) and 0.0006) and	d speech d epileps	delay (sy (p=0.	(33.3%). 04).			
References															
1. Bahi-Buisson N, Roz	ze E, Dionisi C, Esco	ande F, Valayann	nopoulos V, Fe	illet F, etal. Neurologic	al aspects of hyperi	insulinism-hy	perammonaemia syndrome. De	ev Med Child	Nneurol 2008; 50)(12):945-9.					

Risk fa	ctors asses	sment for	r neuro-c	development	al disorders	5	R	isk facte	ors assessn	nent for	epileps	У	
Mann-Whitney U test				Fisher P test	Mann-Whitney	Fisher P test							
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Early age o (p-value	of presentati 0.0006) wer	on (p-valu e associate	12 er	Mutation in Exon 11 and 12 seems to be associated with epilepsy p-value 0.04									
					С	onclusi	on						
> Neuro-dev	velopmenta	al disorde	rs were	seen in 66.7%	% of our coh	ort.							
> Epilepsy (37.5%) was	the most	t commo	n neurologic	al disorder f	followe	d by learning diffic	culties (33.3%) and	l speech	ı delay (33.3%).	
Mutation	in exon 11	and 12 se	ems sigr	nificant risk f	actor for ne	uro-dev	, Jelonmental disord	ter (n=C	,) ()()(6) and	1 enilen:	sv(n=0)) 14)	
								-0.04		· cpiicp:	y (p=0.	547.	
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References 1. Bahi-Buisson N, Ro	oze E, Dionisi C, Esco	ande F, Valayanr	nopoulos V, Fei	illet F, etal. Neurologic	cal aspects of hyperi	insulinism-hy	perammonaemia syndrome. De	ev Med Child	Nneurol 2008; 50	(12):945-9.			

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