Pediatric Neuropsychology Genetic Consultation: Rare de novo GCK Mutation with Severe Persistent Congenital Hyperinsulinemia (CH/CHI)

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Literature Review

Chromosomal abnormalities may result in neurodevelopmental delay. Mutations in the gene encoding the enzyme glucokinase (GCK) have been shown to result in congenital hyperinsulinemia (CH/CHI) and hypoglycemia (Galcheva et al., 2019). GCK is important for both glucose metabolism and homeostasis (Kraslow et al., 2021).

Referral Information

The present case involves a 5-year-old, right-handed, Caucasian male, with a history of GCK who was referred for a neuropsychological evaluation to determine the extent of neurocognitive difficulties including problems with attention, hyperactivity, impulse control, verbal/physical aggression and low frustration tolerance.

Significant Medical and Psychological History

The patient had a history of congenital hyperinsulinemia (CH/CHI), hypoglycemia, de novo GCK dominant pathogenic variant, obstructive sleep apnea, adenoidectomy, myringotomy and tubes, hypertrichosis, ear infections, stertorous respiration, eczema, anemia, tachypnea, environmental allergies, gross motor delay, iron deficiency, vitamin D deficiency, forceps delivery due to macrosomia complicated by shoulder dystocia and right arm brachial plexus injury. At birth, he was reported to be limp and apneic. His APGARS were 1/5/7, he required resuscitation of PPV and then CPAP, and endured a NICU stay of 6.5 weeks.

Neuropsychological Testing Behavior

The patient arrived to testing sessions on time and accompanied by his mother. He exhibited high distractibility and needed cues to remain on task. The patient was generally able to be redirected during moments of impulsivity and excessive motoric activity. He was observed to exhibit physical threats and hitting behavior towards his mother in the waiting room and escalating irritability towards the examiners at times. During the second testing session, he exhibited extreme restlessness, needed a significant amount of encouragement and frequent breaks. His mother reported that he was experiencing glycemic fluctuations. The patients mother noted that he can drop glucose levels without warning and he becomes tired and "shuts down." The patient's mood varied from being euthymic to irritable and his affect was generally congruent with mood. His speech was generally fluent. Language was sometimes appropriate but could be verbose and tangential. He displayed variable and inconsistent eye contact during testing sessions, particularly when the examiner was trying to get his attention by calling his name.

Genetic Testing Results

DNA sequence analysis performed by PCR amplification of highly purified genomic DNA, followed by automated bi-directional DNA sequencing of coding regions of the genes revealed:

GCK Variant 1:	Transition T > C
Nucleotide position:	295
Codon position:	99
Amino acid change:	Tryptophan>Arginine
DNA variant type:	Disease-associated mutation, heterozygous
Inheritance:	Autosomal Dominant
Phenotype:	CH

Neuropsychological Testing Result Highlights

Table 1
Reitan Indiana Neuropsychological Battery

	Mean for Non-Impaired Subjects	Mean for Brain-Impaired Subjects	Patient	Cut-off Score
Level of Performance	19.55	42.24	38	31/32
Right-Left Differences	7.21	17.21	15	11/12
Dysphasia and Related Variables	5.79	19.83	12	10/11
Total NDS	32.52	79.28	65	54/55

Table 2
Kaufman Brief Intelligence Test (K-BIT)

	Raw Score	Standard Score	Percentile	Performance
Vocabulary	20	93	32	Average
Matrices	8	73	4	Well Below Average
K-BIT IQ Composite	-	166	10	Below Average

Table 3
California Verbal Learning Test-Children's Version (CVLT-C)

	Raw Score	Scaled Score		Raw Score	Scaled Score
List A Total Trials 1-5	8	27	Semantic Cluster Ratio	1.4	0.5
List A Trial 1 Free Recall	3	-0.5	Serial Cluster Ratio	0.0	-1.0
List A Trial 5 Free Recall	4	-1.0	% of Recall Primacy Region	0	-3
List B Free Recall	0	-2.5	% of Recall Middle Region	25	-1.0
List A Short-Delay Free Recall	0	-2.0	% of Recall Recency Region	75	5.0
List A Short Delay Cued Recall	2	-1.5	Learning Slope	0.2	-1.0
List A Long Delay Free Recall	4	-1.0	% Recall Consistency	0	-3.0
List A Long-Delay Cued Recall	0	-2.5	Correct Recognition Hits	5	-3.0

Table 4
Wide Range Achievement Test-Fourth Edition (WRAT-4)

	Raw Score	Standard Score	Confidence Interval	Percentile	Grade	Performance
Word Reading	11	92	84-101	30	<K.0	Average
Spelling	8	89	80-89	23	<K.0	Below Average
Math Computation	11	104	93-114	61	K.2	Average

Results

Neuropsychological testing revealed a diagnosis of a neurodevelopmental disorder characterized by an attention-deficit/hyperactivity disorder—combined type, dysexecutive syndrome/executive functioning disorder, below average general intellectual functioning, severe behavioral dysregulation, and problems with encoding and retention of verbal information into memory.

Results Continued

The patient's ability to repeat a list of words the first time he heard it indicates an average initial attention span for auditory-verbal information. On his fifth learning attempt, however, his performance was low average. In addition, his total recall of the word list across the five learning trials was extremely low compared to others his age. The patient's recall of words was extremely low from the beginning of the list, low average from the middle of the list, and significantly elevated from the end of the list; these findings reflect a passive learning style in that an elevated percentage of words that he recalled came from the end of the list. The patient's consistency index was extremely low. Children with problems in consistency may know information one time and not the next; their thoughts may be described as "scattered." Within the first five trials, he reached a learning plateau somewhat faster than others his age did, limiting the number of new words he recalled. When presented with a second interference list, the patient's recall was extremely low. He exhibited an unusually high degree of vulnerability to proactive interference from the first list. After a short delay, the patient's recall of the first list was below average. Following a delay of about 20 minutes, the patient's recall of the first list was low average for his age. Category cueing after the long delay failed to improve subsequent performance. The patient recalled fewer words when provided with the category cues than when recalling words on his own. This suggests that he has difficulty using semantic strategies to remember verbal information.

Conclusions

Rare de novo GCK mutations with severe persistent CH/CHI are uncommon (Kraslow et al., 2021). According to Roper et al. (2020), roughly up to 48% of neonates affected with CH/CHI may exhibit sequelae of neurodevelopmental delay and intellectual disabilities. Hyperinsulinemic hypoglycemia (HH) is a condition characterized by a disproportionate amount of insulin released by the beta cells of the pancreas relative to the plasma glucose level at that time (Kraslow et al., 2021). Mutations in the gene encoding the enzyme glucokinase (GCK) on chromosomes 7 and 12 have been shown to result in both HH and hypoglycemia. GCK is important for both glucose metabolism and homeostasis as it phosphorylates glucose and converts it to glucose-6-phosphate, trapping it in the cell. However, the same gene (GCK) with a gain-of-function mutation causes overactivity of the aforementioned cellular cycle, causing inappropriate insulin release (Kraslow et al., 2021). It is likely that the patient's emotional incontinence and inconsistent performance were influenced by fluctuating glycemic levels. Analyses of GCK mutations and resultant neuropsychological deficits are rarely reported. Our case highlights the importance of pediatric neuropsychology genetic consultation in elucidating neurodevelopmental sequelae as a basis for academic and rehabilitation recommendations.

References

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