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Low CSF 5-HIAA in Myoclonus Dystonia

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Conflicts of Interests related to the study

The authors report no financial disclosures of conflicts of interest.

Introduction

Myoclonus Dystonia (MD) (DYT11) is an early-onset hyperkinetic movement disorder with a prominent psychiatric phenotype caused by mutations in the ϵ -sarcoglycan (*SGCE*) gene. (1) Although its precise function is unknown, multiple studies suggest ϵ -sarcoglycan to be involved in monoamine metabolism and neurotransmission. We report four patients with *SGCE*-mutation-positive MD associated with low cerebrospinal fluid (CSF) levels of the serotonin metabolite, 5-hydroxyindoleacetic acid.

Methods

Cases were ascertained through (i) systematic searches of CSF Neurotransmitter Databases (National Hospital for Neurology and Neurosurgery, UK and University Children's Hospital, Heidelberg, Germany (**Cases 1-3**) and (ii) collaboration with clinicians (**Case 4**). *SGCE* mutation analysis was undertaken in diagnostic laboratories. Lumbar punctures were undertaken during investigation and CSF neurotransmitters analyzed using standardized protocols. CSF levels of the dopamine metabolite, homovanillic acid (HVA), serotonin metabolite, 5-HIAA (5-hydroxyindoleacetic acid) and pterin species were measured by high performance liquid chromatography. Blood serotonin levels were measured for Cases 1-3.

Results

Clinical and genetic characteristics are summarized in Figure 1A. In all cases, CSF 5-HIAA levels were below the lower limit of the normal reference range. All other CSF neurotransmitter metabolites were within normal expected values, except Case 4 where HVA (88nmol/L, age related reference range, ARRR:145-324nmol/L) and tetrahydrobiopterin (6.8nM, ARRR:12-30nM) were also reduced (Figure 1A).

Discussion

We report four patients with *SGCE*-mutation positive MD associated with abnormal CSF 5-HIAA levels. To date, the CSF neurotransmitter profile of MD has not been delineated, as CSF neurotransmitter analysis is rarely undertaken in MD patients. Indeed when MD is clinically suspected, early genetic testing and molecular confirmation of the diagnosis typically negates the need for further clinical investigations.

Isolated cerebral serotonin deficiency is increasingly recognized as a distinct clinical disorder (Figure 1B).(2, 3) A recent study showed ~20% of childhood-onset movement disorders to be associated with reduced CSF 5-HIAA levels, 49% of these demonstrating an isolated CSF 5-HIAA reduction.(4) Serotonin has an important role during neuronal development, influencing cell differentiation and synaptogenesis, and mood and motor control in the mature brain.(5) Alcohol ingestion has also been observed to transiently increase serotonergic neurotransmission in animal models, potentially explaining its beneficial effects in MD.(6) Notably, three patients in our study had normal blood serotonin levels, suggesting that serotonin dyshomeostasis in MD may be tissue-specific.

In contrast, the *Sgce* KO mouse model found no reduction in striatal serotonin and 5-HIAA levels compared to controls, although elevated HVA levels were inversely correlated with 5-HIAA levels.(7) This discrepancy may be due to inherent differences between striatal tissue and CSF, or possible region specific changes in the rodent brain.

Reduced CSF HVA was observed in Case 4, with values towards the lower end of the normal range in Cases 1-3, a feature also seen in patients with primary neurotransmitter disorders (e.g. tyrosine hydroxylase deficiency) (Figure 1B), depression and alcoholism.(8, 9) As only one patient in our series had a definitively abnormal HVA level, its relevance in MD remains unclear.

Our report suggests a possible link between MD and impaired brain serotonin homeostasis. Underlying mechanisms potentially include impaired cerebral serotonin production, metabolism or transport. Although not suggested as a routine investigation, it may be a useful future disease biomarker, which may guide biological models and provide a target for drug development.

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Case	Current age	Age at clinical presentation	Myoclonus	Dystonia	DSM-IV Psychiatric disorders	Response to treatment	Response to treatment with SSRI	Family History	SGCE mutation	Age at lumbar puncture	Cerebrospinal Fluid			Serum Serotonin (500-1600nmol/L)
											HIAA (ARRR)	HVA (ARRR)	Pterin profile (ARRR)	
1	18 years	1.5 years	UL, LL Trunk	UL & LL	GAD	1. Clonazepam (worsening of motor & psychiatric symptoms)	No marked improvement to anxiety symptoms with Fluoxetine (20mg)	Nil reported No maternal/paternal DNA available for testing	c.289C>T p.Arg97Ter	15 years	47 (58-220nmol/L)	195 (71-565nmol/L)	Normal	1597
2	26 years	Childhood	Neck, UL, Trunk	Neck & UL	GAD	1. Tiapride (good response, stopped following oculogyric crisis) 2. Primidone (stopped due to drowsiness) 3. Propranolol (no response)	Treatment not tried.	Similar movement disorder reported in multiple paternal relatives	c.835_839del p.Thr279Alafs X17	15 years	21 (58-220nmol/L)	108 (71-565nmol/L)	Normal	1041
3	31 years	10 years	UL & Trunk	Neck & Trunk	GAD, Depression, OCD, Alcohol excess, Social Phobia, Panic Disorder	1. Tiapride (no response) 2. Propranolol (no response) 3. Clonazepam (no response) 4. 5-hydroxy-L-tryptophan (stopped due to GI side effects)	Treatment not tried.	Similar movement disorder reported in multiple paternal relatives	c.835_839del p.Thr279Alafs X17	11 years	49 (58-220nmol/L)	116 (71-565nmol/L)	Normal	1354
4	51 years	7-10 years	Neck, Trunk, UL, LL	Neck	Alcohol excess, Depression	1. Pramipexole (exacerbated myoclonus) 2. Gabapentin (exacerbated myoclonus) 3. Benzodiazepines (stopped due to sedation) 4. Levodopa (stopped due to GI side effects)	Mild to moderate improvement to anxiety with sertraline.	Similar movement disorder reported in father and sister	c.107C>G p.T36R	42 years	55 (79-140nmol/L)	88 (145-324nmol/L)	Total neopterin: 9.4 (7-65nM) Tetrahydrobiopterin 6.8 (12-30nM) SMTHFR 59 (40-170nM)	Not performed.

Figure 1A. Clinical, biochemical and genetic features of patients with SGCE-mutation positive Myoclonus Dystonia

ARRR: Age Related Reference Range, LL: Lower Limbs, UL: Upper Limbs. Values in red: CSF values outside age adjusted reference range.

Figure 1B. Classification of primary and secondary monoamine neurotransmitter disorders

AADC: Aromatic L-Amino Acid Decarboxylase, DAT: Dopamine Transporter, HIE: Hypoxic Ischaemic Encephalopathy, PKAN: Pantothenate kinase associated neurodegeneration, PTPS: 6-Pyruvoyl-Tetrahydropterin Synthase, VMAT2: Vesicular Monoamine Transporter 2.