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Citation for final published version:


Publishers page: http://dx.doi.org/10.1002/mds.27117 <http://dx.doi.org/10.1002/mds.27117>

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Low CSF 5-HIAA in Myoclonus Dystonia

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Word Count for manuscript: 500
Character count for title (including spaces and punctuation): 36
Number of Tables/Figures: 1
Number of References: 7

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1
Running Title: Low CSF 5-HIAA in Myoclonus Dystonia

Key Words: Dystonia, Cerebrospinal Fluid, Neurotransmitters, Genetics

Financial Disclosures/Conflicts of Interests related to the study
The authors report no financial disclosures of conflicts of interest.

Study Funding
KJP is funded by an Academy of Medical Sciences Clinical Starter Grant and a Life Sciences Research Network Wales Post-Doctoral grant. MED and NS are funded by NINDS 5P01NS087997. MAK is a Wellcome Intermediate Fellow (WT098524/Z/12/Z).
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.
Authors’ Roles
Kathryn J Peall: 1) Research project (a. conception, b. organization, c. execution), 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)
Joanne Ng: 1) Research project (a. conception, b. organization, c. execution), 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)
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Manju A Kurian: 1) Research project (a. conception, b. organization, c. execution), 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)

Financial Disclosures (for the preceding 12 months)
KJP is funded by an MRC Clinician-Scientist Fellow, and is supported by an Academy of Medical Sciences Clinical Starter Grant and a Life Sciences Research Network Wales Post-Doctoral grant. MED and NS are funded by NINDS 5P01NS087997. JN is an MRC Research Training Fellow. MAK is a Wellcome Intermediate Fellow (WT098524/Z/12/Z). No other financial disclosures are reported for the preceding 12 months.
References


Legends to Figure 1

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

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