

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/103168/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Peall, Kathryn, Ng, Joanne, Dy, Marisela E, Sharma, Nutan, Pope, Simon, Heales, Simon, Friedman, Jennifer R. and Kurian, Manju A 2017. Low CSF 5-HIAA in myoclonus dystonia. *Movement Disorders* 32 (11) , pp. 1647-1649. 10.1002/mds.27117 file

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

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Low CSF 5-HIAA in Myoclonus Dystonia

Kathryn J Peall (MD, PhD),^{1*} Joanne Ng (MD),^{2,3*} Marisela E Dy (MD),^{4,5}
Nutan Sharma (MD, PhD),⁵ Simon Pope (PhD),⁶ Simon Heales (PhD),^{6,7}
Jennifer R. Friedman (MD, PhD),⁸ Manju A Kurian (MD, PhD)^{2,3}

¹MRC Centre for Neuropsychiatric Genetics and Genomics, Hadyn Ellis Building, Heath Park, Cardiff, UK CF24 4HQ

²Developmental Neurosciences, UCL Great Ormond Street-Institute of Child Health, London, UK

³Department of Neurology, Great Ormond Street Hospital, London, UK

⁴Department of Neurology, Boston Children's Hospital, Boston, USA

⁵Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA

⁶Neurometabolic Unit, The National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

⁷Centre for Translational Omics, UCL Great Ormond Street, Institute of Child Health, 30 Guildford Street, London

⁸Departments of Neurosciences and Pediatrics, UC San Diego School, Rady Children's Hospital and Rady Children's Institute for Genomic Medicine, San Diego, USA

*These authors contributed equally to the manuscript

Word Count for manuscript: 500

Character count for title (including spaces and punctuation): 36

Number of Tables/Figures: 1

Number of References: 7

Corresponding Authors:

Dr Kathryn Peall, MRC Centre for Neuropsychiatric Genetics and Genomics, Hadyn Ellis Building, Heath Park, Cardiff, UK CF24 4HQ. Tel: +44 29 20 688353 Email: PeallKJ@cardiff.ac.uk

Dr Manju Kurian, Developmental Neurosciences, UCL Great Ormond Street-Institute of Child Health, London, UK. Tel: 020 7405 9200 (ext. 8308) Email: manju.kurian@ucl.ac.uk

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)

Marisela E Dy: 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)

Nutan Sharma: 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)

Simon Pope: 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)

Simon Heales: 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)

Jennifer R Friedman: 2) Data (analysis or interpretation of the data), 3) Manuscript (A. writing of the first draft, b. review and critique)

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

1. Peall KJ, Smith DJ, Kurian MA et al. SGCE mutations cause psychiatric disorders: clinical and genetic characterization. *Brain*. 2013;136(Pt 1):294-303.
2. Assmann B, Kohler M, Hoffmann GF, Heales S, Surtees R. Selective decrease in central nervous system serotonin turnover in children with dopa-nonresponsive dystonia. *Pediatr Res*. 2002;52(1):91-4.
3. Meyer E, Carss KJ, Rankin J et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. *Nat Genet*. 2017;49(2):223-37.
4. De Grandis E, Serrano M, Perez-Duenas B et al. Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid, in neurological disorders. *J Inherit Metab Dis*. 2010;33(6):803-9.
5. Herlenius E, Lagercrantz H. Neurotransmitters and neuromodulators during early human development. *Early Hum Dev*. 2001;65(1):21-37.

6. LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse, and dependence: findings of animal studies. *Biol Psychiatry*. 1994;36(6):395-421.
7. Yokoi F, Dang MT, Li J, Li Y. Myoclonus, motor deficits, alterations in emotional responses and monoamine metabolism in epsilon-sarcoglycan deficient mice. *J Biochem*. 2006;140(1):141-6.
8. Sher L, Oquendo MA, Li S et al. Lower CSF homovanillic acid levels in depressed patients with a history of alcoholism. *Neuropsychopharmacology*. 2003;28(9):1712-9.
9. Willemsen MA, Verbeek MM, Kamsteeg EJ et al. Tyrosine hydroxylase deficiency: a treatable disorder of brain catecholamine biosynthesis. *Brain*. 2010;133(Pt 6):1810-22.

Legend to Figure 1

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.