Child Neurology Open
Volume 10: 1-4

DOI: 10.1177/2329048X231184183
journals.sagepub.com/home/cno

Broadening the Spectrum of *SLC22A5* Phenotype: Primary Carnitine Deficiency Presenting with Focal Myoclonus

Maymunah Khries, MBBS, MA[1], Albert Lim, MBBS, MA[1], Dipayan Mitra, MBBS, MD, FRCR[2], Mark Anderson, BSc, BMedSci, BM, BS[3], Jan Bengtsson, MD, PHD[4], Ann Bowron, BSc, MSc, PHD, FRCPath[5], Elizabeth Harris, MBBS, MSc[6], Jessica Blickwedel, BSc, MBChB, MSc[1], Karen Wood, MBBS[1], and Anna P. Basu, BMBCh, MA, FRCPCH, PHD[1,7]

Abstract

Primary carnitine deficiency (PCD) is caused by pathogenic variants of the *SLC22A5* gene, which encodes a transmembrane protein that functions as a high affinity carnitine transporter. Carnitine is essential for the transport of acyl-CoA, produced from fatty acids, into the mitochondria where they are oxidised to produce energy. We present the case history of an 8-year-old boy who presented with fever, lethargy, focal rhythmic (3 Hz) left wrist twitching, and severe encephalopathy. MRI brain showed basal ganglia involvement. Metabolic investigations revealed low serum carnitine; whole genome sequencing confirmed compound heterozygous *SLC22A5* mutations. With carnitine replacement, intensive care support, and neurorehabilitation, he made a remarkable recovery, regaining independent breathing, speech, mobility, and hand use. Seizure presentation in PCD is rare and presentation with sustained focal myoclonus has not been previously reported. This case expands the known phenotype of PCD. Prompt carnitine replacement is imperative.

Keywords

primary carnitine deficiency, focal myoclonus, genotype phenotype

Received April 8, 2023. Accepted for publication June 7, 2023.

Introduction

Mutations in the *SLC22A5* gene on chromosome 5q31 cause primary carnitine deficiency (PCD) due to deficiency of organic cation transporter 2 (OCTN2), resulting in urinary carnitine loss, low serum carnitine and intracellular carnitine depletion.[1] Carnitine is essential for the transport of acyl-CoA, produced by the action of acyl-CoA synthases on fatty acids, across the mitochondrial inner membrane. Lack of carnitine impairs beta-oxidation of fatty acids, an essential source of energy and ketogenesis during periods of fasting or metabolic stress, increasing susceptibility to 'decompensated crises'.

PCD can manifest with a range of symptoms. While cardiac symptoms are the most prevalent (23.8%), 7.1% of patients present with neurological symptoms including (rarely) seizures (0.3%) and encephalopathy (0.3%).[2] Onset of neurological symptoms is usually in early childhood. Here we report a case of PCD presenting with refractory focal myoclonus.

Case Presentation

A previously well 8-year-old boy presented with fever, vomiting, confusion, lethargy and focal repetitive left wrist twitching,

[1]Paediatric Neurology, Great North Children's Hospital, Newcastle upon Tyne, UK
[2]Neuroradiology, Great North Children's Hospital, Newcastle upon Tyne, UK
[3]Paediatrics, Great North Children's Hospital, Newcastle upon Tyne, UK
[4]Paediatric Intensive Care Unit, Great North Children's Hospital, Newcastle upon Tyne, UK
[5]Metabolic Biochemistry, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[6]Northern Genetics Service, Centre for Life, Newcastle upon Tyne, UK
[7]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK

Corresponding Author:
Anna Purna Basu, Level 3, Sir James Spence Institute, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK.
Email: anna.basu@newcastle.ac.uk

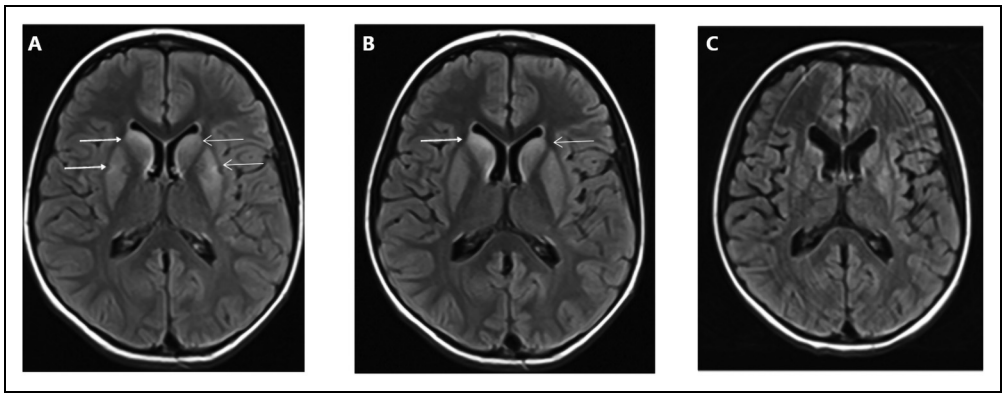

Figure 1. MRI head. A, Day 1 of PICU admission. Subtle bilateral high signal in the lentiform and caudate nuclei (arrows), swelling of the caudate nuclei, no restricted diffusion, contrast enhancement. MRS was non-specific (not shown). B, Day 5. Persistent basal ganglia changes, mild reduction in swelling of the caudate nuclei with reduced mass effect on the frontal horns of the lateral ventricles (arrows). C, Two months later, showing resolution of basal ganglia signal changes and swelling; frontal horns of lateral ventricles no longer compressed, but mild basal ganglia atrophy.

preceded by 4 days of fever and malaise. He was drowsy and encephalopathic. He was treated empirically for infection, intubated and transferred to PICU.

Initial treatment covered possible infective or autoimmune encephalitis. He received high dose intravenous methylprednisolone, plasmapheresis, intravenous immunoglobulin and, following local consensus, anakinra for possible febrile epilepsy related syndrome (FIRES). Despite multiple anticonvulsants, the focal abnormal movement, phenotypically consistent with epilepsia partialis continua (EPC), was difficult to suppress. Serial electroencephalograms (EEG) did not capture a seizure focus. However, when his sedation (midazolam infusion) and phenobarbitone were reduced, the abnormal movements spread to involve the left big toe, tongue and face. The movement was refractory to all treatment except high dose barbiturates - these were weaned once it was possible to do so without incurring spread beyond the left wrist.

Investigations

Extensive investigations were undertaken, including baseline biochemistry, metabolic, genetic, autoimmune, and neuromuscular investigations. There was no evidence of autoimmune encephalitis, nor of mitochondrial disease despite sequencing of the polymerase gamma (POLG) panel and common mitochondrial DNA mutations plus the mitochondrial genome and undertaking MRI with spectroscopy. Blood and CSF lactate were normal.

Imaging

Echocardiography and abdominal ultrasound were normal. MRI brain at presentation showed subtle symmetrical signal changes around the basal ganglia and hippocampi, but no cortical abnormality (Figure 1A). Repeat imaging four days later showed more obvious FLAIR hyperintensity of the caudate and putamen (Figure 1B). MR spectroscopy demonstrated reduced NAA in the left basal ganglia (a non-specific finding). Two months later, the signal intensity and swelling of the putamina and caudate nuclei had significantly reduced though there was mild atrophy of the basal ganglia (Figure 1C).

Neurophysiology

Multiple EEGs did not capture epileptiform activity despite refractory focal myoclonus.

Metabolic and Immunological Investigations

Metabolic investigations requested shortly after admission included acylcarnitine profile (blood spot) – this identified low free carnitine, confirmed by measurement of plasma free carnitine on three separate samples. The initial plasma free carnitine was low at 2.7 μmol/l (reference range 23-52) with increased fractional excretion of free carnitine at 29% (reference range < 2%) (Table 1). There was no evidence of impaired renal tubular function.

Genetic Results

Rapid exome sequencing confirmed primary carnitine transporter deficiency, with compound heterozygosity for a pathogenic c.136C > T (p.Pro46Ser) and a likely pathogenic c.2T > G (p.Met1) *SLC22A5* missense and translation initiation codon variant. There was also an incidental finding of Klinefelter syndrome.

Clinical Progress

The patient was started promptly on carnitine replacement therapy, which marked the start of his improvement. He was transferred out of PICU after one month but was extremely weak, with muscle wasting, and required respiratory support and nasogastric tube feeding. With carnitine replacement, supportive management, and therapy team input, he made a remarkable recovery, and his plasma carnitine and acylcarnitine profile normalised.

Table 1. Summary of key Metabolic and Immunological Investigation Results.

Investigation	Result	Reference Range
Metabolic		
Blood spot free carnitine (initial result which prompted further investigation)	**4.7** umol/L	13-44
Plasma free carnitine	**2.7** umol/L	23-52
Plasma Total carnitine	**3.7** umol/L	27-63
Plasma acylated carnitine	**28%**	0-40
Urine free carnitine	6 mmol/L	3-146
Urine total carnitine	25 mmol/L	12-294
Urine acylated carnitine	**76%**	20-75%
Fractional excretion of carnitine	**29%**	< 2%
Plasma amino acids profile	Normal	N/A
Urine amino acids profile	Normal	N/A
Urine organic acids profile	Normal	N/A
Blood pyruvate	0.03 mmol/L	0.035-0.15
Blood lactate/pyruvate ratio	21	0-18
Lysosomal enzyme profile	Normal	
Very long chain fatty acids	Normal	
CSF/plasma glycine ratio	**0.025***	<0.02
CSF lactate	1.24 mmol/L	0-1.8
CSF protein	0.3 g/L	0-0.4
Serum caeruloplasmin	0.24 g/L	0.15-0.45
Serum copper	16.3 µmol/L	11.1-27.4
Immunological		
ANA and ANA related antibodies	Negative	N/A
Glycine receptor antibodies	Negative	N/A
anti-basal ganglia antibody	Negative	N/A
acetylcholine receptor antibody	Negative	N/A
Purkinje cell antibody	Negative	N/A
Anti-GAD antibody	Negative	N/A
Anti-neuronal nuclear antibody	Negative	N/A
**Paired anti CASPR2, anti LGI-1	Negative	N/A
**Paired immunology cytokines (IFN gamma, TNF alpha, IL10, IL6, IL4, IL2)	<50 pg/ml	<50 pg/ml
**Paired oligoclonal bands	Negative	N/A
CSF Aquaporin 4 antibody, MOG antibody, NMDA receptor antibody	Negative	N/A
CSF anti-AMPA1, anti-AMP2, anti-GABAb	Negative	N/A
CSF glycine receptor antibody	Negative	N/A
CSF anti-basal ganglia antibody	Negative	N/A
CSF anti-amphiphysin, anti CRMP5, anti GAD65, anti HU, anti MA1, anti MA2, anti Ri, anti SOX1, anti Tr, anti Yo, anti Zic4 antibody	Negative	N/A

*Not consistent with classical non-ketotic hyperglycinaemia.
**Paired: CSF and Serum Samples.
N/A: Not applicable.

At discharge from hospital (four months after his presentation), he remained mildly weak. He could walk short distances but tired easily. He had mild extrapyramidal symptoms, with low amplitude, high frequency left wrist tremor, which did not impede function. He also had some behavioural and concentration issues which were managed with atomoxetine in the short term and improved over time. He continued carnitine supplementation (100 mg/kg/day). Further improvement was observed with community follow-up though the wrist tremor persisted. Cardiac assessment 6 months after his initial presentation revealed mildly impaired ventricular function with ejection fraction of 50–55% but normal fractional shortening (30%).

Discussion

Biallelic pathogenic *SLC22A5* variants cause systemic PCD. Based on the evidence classification using the American College of Medical Genetics and Genomics (ACMG), the Association for Molecular Pathology (AMP)[3] and Association for Clinical Genomic Science (ACGS) 2020 guidelines (uk-practice-guidelines-for-variant-classification-v4-01-2020.pdf (acgs.uk.com)), the "likely pathogenic" variant noted in our patient results in loss of the initiation codon (PVS1_Moderate). A different nucleotide change, also resulting in loss of the initiation codon, was reported in another patient with systemic primary carnitine deficiency (PS1_Moderate). The variant in our patient has not been reported in the gnomAD database (>15 000 individuals) (PM2_Moderate).

The c.136C > T mutation is one of the most frequent allelic mutations detected in PCD.[4] Patients with this mutation (p.P46S) may be asymptomatic or experience only mild symptoms.[4–6] Phenotypes reported with this variant include ventricular arrhythmias,[5] prolonged QT interval,[5,7] fasting intolerance,[5] fatiguability,[5] transient developmental delay and mildly reduced muscle strength.[8]

This case highlights a presentation of carnitine transporter deficiency which to our knowledge has not been described previously. The presentation clinically resembled that of refractory focal myoclonus in children with mitochondrial disorders including EPC. EPC is classified by the International League Against Epilepsy (ILAE) as a variant of focal motor status epilepticus. It is characterised by frequent, repetitive, often arrhythmic muscle jerks that can continue over a prolonged period.[9] The commonest causes in childhood are Rasmussen encephalitis and mitochondrial disorders.[10] In some cases the cause remains unknown despite extensive investigation. A normal EEG is unusual but cannot exclude EPC, as the seizure focus may be subcortical.[11] EPC can be highly refractory to medical management. It is noteworthy that this child's myoclonus only started to improve following carnitine supplementation.

Basal ganglia damage has been previously reported in acquired encephalopathy due to carnitine deficiency.[12] The manifestation of refractory seizures and the basal ganglia involvement in this case resembled mitochondrial disorders (POLG and Leigh disease respectively).[13] One plausible explanation for these similarities is the role of the carnitine transporter OCTN2 in the mitochondrial beta-oxidation pathway and ATP synthesis. This sodium dependent transporter actively moves L-carnitine intracellularly.[1] The

intracellular carnitine subsequently participates in an enzymatic shuttle system, transporting fatty acids into the mitochondrial matrix. The fatty acids undergo beta-oxidation, generating ATP, the currency of cellular energy. The *POLG* enzyme plays a vital role in the replication and repair of mitochondrial DNA (mtDNA). Deficiency in POLG activity results in mtDNA depletion and reduced activity in the electron transport chain that generates ATP.[14] The common denominator between these two conditions is defective ATP generation.

Conclusion

This case report expands the known phenotype of PCD. Prompt treatment with carnitine replacement plays a significant role in halting and preventing debilitating morbidity in PCD; an early metabolic screen including acylcarnitine profile is critical in patients presenting with encephalopathy and focal myoclonus.

Acknowledgements

We would like to thank the patient and family for their support of this submission including written informed parental consent for publication.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received financial support for the research, authorship, and/or publication of this article: Funding for publication of this report was provided by Newcastle Hospitals Charity (Grant SA1323).

ORCID iD

Anna P. Basu https://orcid.org/0000-0002-1356-3027

References

1. Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. *Biochim Biophys Acta*. 2016;1863(10):2422-2435. doi:10.1016/j.bbamcr.2016.01.023
2. Crefcoeur LL, Visser G, Ferdinandusse S, Wijburg FA, Langeveld M, Sjouke B. Clinical characteristics of primary carnitine deficiency: A structured review using a case-by-case approach. *J Inherit Metab Dis*. 2022;45(3):386-405. doi:10.1002/jimd.12475
3. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30
4. Li FY, El-Hattab AW, Bawle EV, et al. Molecular Spectrum of SLC22A5 (OCTN2) gene mutations detected in 143 subjects evaluated for systemic carnitine deficiency. *Hum Mutat*. 2010;31(8):E1632-E1651. doi:10.1002/humu.21311
5. Schimmenti LA, Crombez EA, Schwahn BC, et al. Expanded newborn screening identifies maternal primary carnitine deficiency. *Mol Genet Metab*. 2007;90(4):441-445. doi:10.1016/j.ymgme.2006.10.003
6. Rose EC, di San Filippo CA, Ndukwe Erlingsson UC, Ardon O, Pasquali M, Longo N. Genotype-phenotype correlation in primary carnitine deficiency. *Hum Mutat*. 2012;33(1):118-123. doi:10.1002/humu.21607
7. De Biase I, Champaigne NL, Schroer R, Pollard LM, Longo N, Wood T. Primary carnitine deficiency presents atypically with long QT syndrome: A case report. *JIMD Rep*. 2012;2:87-90. doi:10.1007/8904_2011_52
8. de Boer L, Kluijtmans LA, Morava E. Primary carnitine (OCTN2) deficiency without neonatal carnitine deficiency. *JIMD Rep*. 2013;10:39-40. doi:10.1007/8904_2012_198
9. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus - report of the ILAE task force on classification of Status epilepticus. *Epilepsia*. 2015;56(10):1515-1523. doi:10.1111/epi.13121
10. Surana S, Rossor T, Hassell J, et al. Diagnostic algorithm for children presenting with epilepsia partialis continua. *Epilepsia*. 2020;61(10):2224-2233. doi:10.1111/epi.16650
11. Mameniskiene R, Wolf P. Epilepsia partialis continua: A review. *Seizure-Eur J Epilep*. 2017;44:74-80. doi:10.1016/j.seizure.2016.10.010
12. Kim H, Chu K, Jung KH, Lee ST, Kim JM, Lee SK. Acquired encephalopathy associated with carnitine deficiency after cefditoren pivoxil administration. *Neurol Sci*. 2012;33(6):1393-1396. doi:10.1007/s10072-012-0939-7
13. Anagnostou ME, Ng YS, Taylor RW, McFarland R. Epilepsy due to mutations in the mitochondrial polymerase gamma (POLG) gene: A clinical and molecular genetic review. *Epilepsia*. 2016;57(10):1531-1545. doi:10.1111/epi.13508
14. Naviaux RK, Nyhan WL, Barshop BA, et al. Mitochondrial DNA polymerase gamma deficiency and mtDNA depletion in a child with Alpers' syndrome. *Ann Neurol*. 1999;45(1):54-58.