DCTN1 Mutation Associated Parkinsonism: Case Series of Three New Families with Perry Syndrome

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Introduction

Mutations in the *DCTN1* gene cause the Perry syndrome: an autosomal dominant form of heredodegenerative parkinsonism, accompanied by neuropsychiatric symptoms, profound weight loss, and later, ventilatory dysfunction [1]. Perry syndrome is rare, having been reported in 32 families worldwide [2], but early recognition of this syndrome is particularly important since intervention in the form of ventilatory support can improve life expectancy [3]. Here we discuss three unrelated individuals with genetically confirmed Perry syndrome associated with autosomal dominant family histories of parkinsonism.

Family 1

A 40 year old female presented with a two year history of reduced oral intake and unintentional weight loss with associated low mood, for which she had been started on mirtazapine (Case I-1). Her presenting symptoms were initially attributed to depression in the context of the breakdown of a long-term relationship. She had felt unsteady when walking for a few months. There were no anosmia, hallucinations, dream enactment or vivid dreams, but she reported difficulty in falling asleep.

Her body mass index (BMI) was 15. She had a blunted affect, and an asymmetrical rest tremor. Rigidity was present in all limbs, with cog-wheeling and symmetrical bradykinesia in the arms. She was hypomimic. There was dystonic posturing in the right first toe. There were no significant cognitive deficits (Addenbrooke's Cognitive Examination-III score 93/100).

Her past medical history included irritable bowel syndrome and endometriosis. Her father had died in his fifth decade with a diagnosis of Parkinson's disease, as had her half-sister. She had two children aged 21 and 19, both of whom remained well (Fig 1).

She was commenced on carbidopa/levodopa which led to an initial improvement in mobility. She subsequently developed dyskinetic movements in the right hand, head and oro-facial region, whilst taking a daily levodopa equivalent dose of 350mg. Overnight oximetry was satisfactory, with an average

nocturnal oxygen saturation of 95%, and only 13 reductions of 4%. Spirometry showed normal lung volumes with forced vital capacity 95%, and forced expiratory volume 106% of the predicted values respectively. MRI brain scan was unremarkable.

She was found to be heterozygous for a pathogenic missense variant in the *DCTN1* gene (c.212G>C p.(Gly71Ala)), consistent with a diagnosis of Perry syndrome. One of her children is currently receiving genetic counselling with a view to arranging predictive testing.

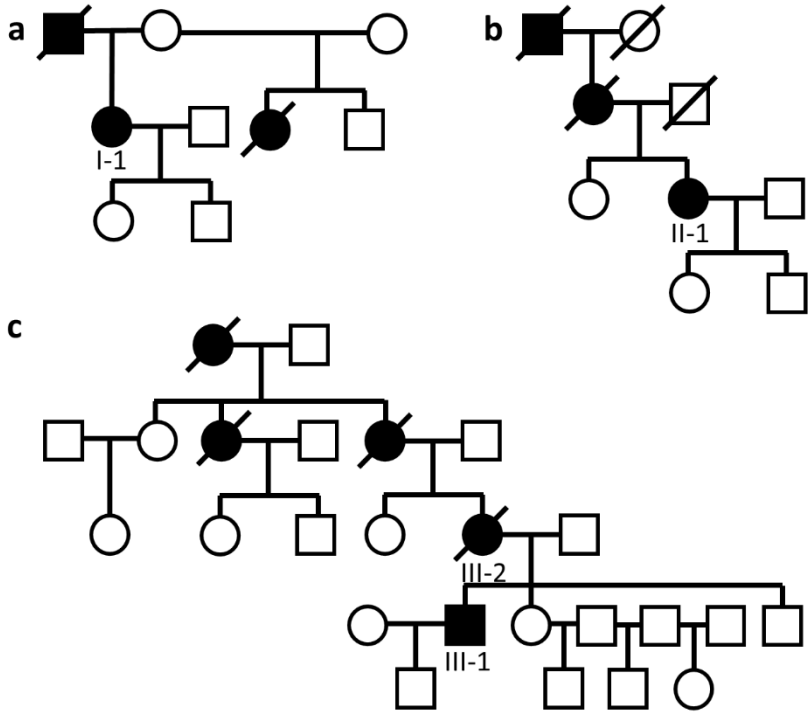

Fig 1 *Family pedigrees of three new UK families with Perry syndrome.* Family history of Parkinsonism shown for family 1 (a), family 2 (b) and family 3 (c). Circles represent females and squares indicate males. Black indicates those with a diagnosis of Parkinson's disease or progressive supranuclear palsy. Cases I-1, II-1 and III-1 are those with genetically confirmed Perry syndrome. Lines indicates individuals that are known to have died

Family 2

A 46 year old female presented with a two year history of unexplained backwards falls, slowed movements, and hypophonia, associated with unintentional weight loss (Case II-1). Her mother had been diagnosed with progressive supranuclear palsy (PSP), with a partial levodopa response, and her maternal grandfather had been diagnosed with possible PSP, both in their sixth decade (Fig 1). Her mother died aged 58 due to a large left middle cerebral artery stroke, but further details about her clinical course are not available. Her sister and two children were well.

On examination there was global and symmetrical akinesia with axial rigidity, though with preserved postural reflexes. Vertical saccades were initially slow, and frontalis hyperactivity was noted. She subsequently developed a supranuclear gaze palsy, with restricted voluntary upgaze with preservation of involuntary eye movements. There was no tremor. Her blink reflex was diminished and facial dystonia (risus sardonicus) was also noted.

An MRI brain scan showed areas of T2 hyperintensity in the region of the globi pallidi, with preserved midbrain volume (Fig 2).

She had an excellent response to levodopa/benserazide which was titrated up to 200/50 mg three times daily. She was subsequently noted to have an abnormal breathing pattern, with short periods of rapid shallow breathing, alternating with periods of normal ventilation. She had attributed this to increasing anxiety. About six months after her initial assessment, she had developed insomnia, requiring treatment with zopiclone. She had continued to lose weight, which dropped by 13 kg over twelve months, resulting in a BMI of 19 kg/m^2. There was no evidence of hypopnoea on overnight oximetry (apnoea hypopnea index 0.1/hr of sleep, average oxygen saturation of 96% with minimum 89%).

Genetic analysis demonstrated a heterozygous pathogenic variant in the *DCTN1* gene (c.211G>A p.(Gly71Arg)), and she was diagnosed with Perry syndrome.

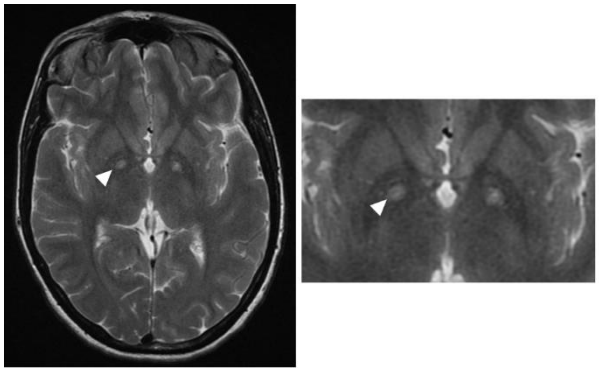

Fig 2 *MRI brain for case II-I.* Bilateral T2-weighted signal hyperintensities were seen in the globi pallidi (white arrowhead)

Family 3

A 37 year old man presented with a 9 month history of asymmetrical tremor, worse on the right side and mostly noticed in the upper limbs (case III-1). His gait had become slower and he reported reduced manual dexterity and micrographia. He had developed low mood and difficulty in getting to sleep, also with frequent waking during the night.

His mother, maternal grandmother (who died aged 68), great-aunt, and great-grandmotherhad all died with diagnoses of Parkinson's disease (Fig 1).

On examination, the right arm displayed cogwheel rigidity, and bradykinesia, with reduced arm swing when walking. There was a subtle action and postural tremor, but no obvious rest tremor.

An MRI brain scan was normal, but DaTscan showed asymmetric severely reduced uptake in the basal ganglia, more marked on the left (Fig 3).

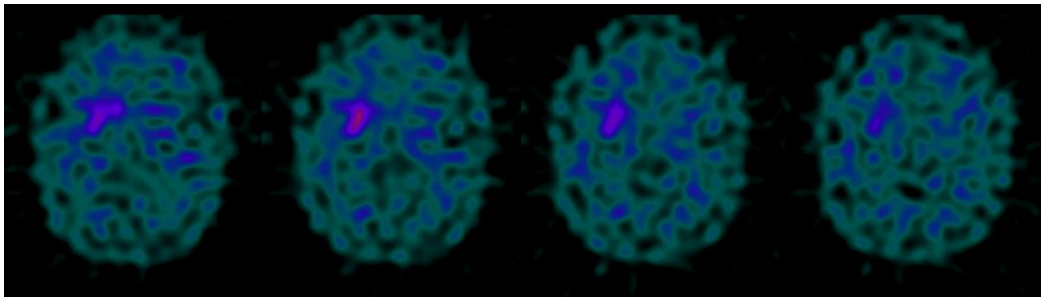

Fig *3 DaT scan for case III-1.* Severe reduction in tracer uptake, more marked on the left side

He was started on carbidopa/levodopa which brought a modest improvement in tremor. He had become less communicative and had developed hypersexuality, irritability and apathy, and his carbidopa/levodopa was withdrawn and replaced with levodopa/benserazide. This led to some benefit, but he developed end-of-dose wearing off spells. At this stage he reported that his appetite had diminished, and he had lost 13 kg over one year.

A genetic test identified that he was heterozygous for a pathological missense variant mutation in the *DCTN1* gene c.212G>C p.(Gly71Ala).

The mother of case III-1 presented aged 47 with a one year history of intermittent left arm tremor, stooped posture, and progressively worsening mobility (case III-2). She had a flattened affect, was hypomimic, and had mild left upper limb parkinsonism with cogwheel rigidity, bradykinesia and rest tremor. She had a background of epilepsy with myoclonic jerks and generalised tonic-clonic seizures, for which she was taking sodium valproate, which was withdrawn, without any improvement in her motor symptoms.

She was commenced on pramipexole, which brought improvement in the tremor, but little effect on her other symptoms. Levodopa was introduced, to which she had a moderate response, though with subsequent development of problematic end-of-dose wearing off spells, characterised by stiffness, bradykinesia, drooling and left leg tremor. She developed a tendency to gambling and online shopping, so pramipexole was withdrawn.

Her motor disorder progressed gradually with development of postural instability, and she was admitted to a nursing home. She developed daytime somnolence and anxiety, and died aged 54 due to urinary sepsis, without undergoing genetic analysis.

Discussion

Here we report on three unrelated individuals from the same region of the United Kingdom, with genetically confirmed Perry syndrome, representing three new families with the condition.

Typical features of Perry syndrome include an akinetic-rigid movement disorder associated with weight loss, depression, apathy and hypoventilation [1]. In addition to these cardinal features, sleep disturbance is common, and patients may develop cognitive deficits (predominantly in executive function and attention), and autonomic dysfunction [2]. Clinical progression is rapid, with death usually occurring within five years. Response to levodopa is typically poor or transient, though good response has been seen in some individuals [1,3]. All of our cases displayed at least a temporary response to levodopa, but with development of motor complications. Atypical presentations have been reported, including those that resemble PSP [4] or frontotemporal dementia [5]. Other phenotypes of *DCTN1* mutation include familial motor neuron disease and distal hereditary motor neuronopathy type 7b (dHMN7B). These phenotypes do not seem to co-exist with Perry syndrome, though individuals with Perry syndrome, dHMN7B and an overlapping phenotype have been reported in a family from China [6].

Our cases presented with the core phenotype of Perry syndrome, consisting of a movement disorder, with accompanying weight loss and neuropsychiatric symptoms, with an autosomal dominant family history (Table 1). Two of our cases had developed some subtle features of ventilatory dysfunction at the time of assessment, though with satisfactory overnight oximetry recordings. Prominent sleep disturbance was seen in two of the cases. Dystonia occurred in two of our cases, which has not previously been reported.

Case II-1 presented with a PSP-like picture, with symmetrical parkinsonism, absence of tremor, early gait failure and falls, along with an impairment in vertical saccades. Two family members had previously been diagnosed with PSP (a condition which is rarely familial), and though to our knowledge genetic analysis of the *DCTN1* gene was not performed, we assume that their symptoms were due to atypical Perry syndrome.

	Case I-1	**Case II-1**	**Case III-1**	**Case III-2**
Sex	Female	Female	Male	Female
Genetics	c.212G>C	c.211G>A	c.212G>C	NA
Age at symptom onset	38	44	37	46
Family history	+	+	+	+
Motor features	Symmetrical bradykinesia and rigidity Symmetrical tremor Dystonia Levodopa-induced dyskinesia	Symmetrical bradykinesia and rigidity Early falls Facial dystonia	Asymmetrical tremor (kinetic and postural) Asymmetrical bradykinesia and rigidity Eyelid tremor	Asymmetrical tremor Asymmetrical bradykinesia and rigidity Postural instability Stooped posture
Weight loss	+	+	+	Not known
Ventilatory features	+	+	-	Not known
Levodopa response	Short-lived	Good	Modest	Modest
Levodopa-induced dyskinesia	Early	-	-	-
Neuropsychiatric features	Depression	Anxiety	Depression Apathy Hypersexuality (precipitated by levodopa)	Anxiety Flattened affect Impulse control disorder (precipitated by dopamine agonist)

Other features		Impaired vertical saccades Insomnia	Insomnia	Daytime somnolence

Table 1 *Clinical characteristics of new Perry syndrome cases*

To our knowledge, 32 families with *DCTN1* mutation-associated parkinsonism have been described (Canada (n=5), Japan (n=5), United Kingdom (n=4), USA (n=4), Korea (n=3), France (n=2), New Zealand (n=2), Poland (n=2), and Turkey, Taiwan, Colombia, Portugal, and China (all n=1)) [2]. All of our cases carried mutations resulting in a glycine to arginine substitution at codon 71, which is known to be pathogenic, and is the most commonly identified mutation in reported cases. Cases II-1 and III-1 shared the same variant (c.212G>A p.(Gly71Arg)), and though they were not known to be related, it is possible that they share a common distant ancestor.

The identification of three new cases of Perry syndrome (all with previously undiagnosed family members) from a small regional population, highlights the need to consider this condition in patients presenting with early-onset Parkinsonism. Review of data from a MEGAchip array genetic analysis of two community-based incident cohorts of patients with sporadic Parkinson's disease from Cambridgeshire, UK (CamPaIGN and PICNICS [7,8]) identified four benign *DCTN1* non-synonymous variants (G2744A, C1465T, G1082A, G122A) in 15 of 380 patients, but no known pathogenic variants (unpublished data).

The neuropathology of Perry syndrome determined at post-mortem involves neuronal loss and gliosis in the substantia nigra, striatum and locus coeruleus, without Lewy bodies. Other areas of neuronal loss include the globus pallidus, subthalamic nucleus, dorsal Raphe nucleus, pontine reticular formation, periaqueductal grey matter, hypothalamus, and the ventrolateral medulla – the proposed site of the central respiratory centre, possibly accounting for the ventilatory abnormalities seen [2,9]. TAR DNA-binding protein of 43 kDa (TDP43) inclusions are identified in the basal ganglia, with relative sparing of the cortex – a distribution that distinguishes Perry syndrome pathology from other TDP43

proteinopathies [10]. Furthermore, the ultrastructural morphology of TDP43 pathology in Perry syndrome differs from that in other TDP43 proteinopathies, suggesting heterogeneity in the pathogenic mechanisms of these conditions [10]. The most frequent lesion morphologies in Perry syndrome are neuronal cytoplasmic inclusions and dystrophic neurites [10]. Truncated forms of TDP43 with abnormal phosphorylation are also seen [9]. TDP43 inclusions do not occur in HMN7B, but neuronal cytoplasmic inclusions of dynactin subunit p50 (which do not occur in other TDP43 proteinopathies) are seen in both Perry syndrome and HMN7B, suggesting that some of the pathogenic mechanisms of these distinct phenotypes may overlap, to some extent.

The *DCTN1* gene encodes subunit 1 of the dynactin complex, which is involved in the retrograde transport of cargoes along microtubules [11]. This complex also plays a role in trafficking of components of the lysosome-autophagy system in axons (a system which is implicated in the pathogenesis of Parkinson's disease) [12]. Whilst autophagy appears to form an important cellular defence against TDP43-mediated neurodegeneration, TDP43 inclusions have also been shown to impair chaperone-mediated autophagy, and it is possible that *DCTN1* mutations amplify a pathogenic cycle, leading to neuronal loss [13]. Mutations that have been observed in Perry syndrome cluster in exon two of the gene, located within or close to a five amino-acid motif required for microtubule binding. Mutations associated with Perry syndrome and HMN7B generally occur at the N-terminus, whilst those associated with motor neuron disease or fronto-temporal dementia phenotypes are found at the C-terminus, but the precise mechanisms by which phenotype is determined in *DCTN1* mutation carriers is not known [2].

The MRI brain for case II-1 showed symmetrical hyperintensity in the globi pallidi, which has not previously been reported in Perry syndrome. The significance of this is not clear, and similar appearances have been reported to be a physiological finding associated with aging [14]. However, TDP-43-positive axonal spheroids have been identified in the globus pallidus in Perry syndrome patients, raising the possibility that these imaging findings are a correlate of pathology [9]. Imaging in previously reported cases has been relatively unrevealing, though atrophy in fronto-temporal regions

and the midbrain has been seen in some patients [2]. None of our patients were seen to have significant atrophy.

Management of Perry syndrome is supportive. Dopaminergic medications may offer some benefit, but the levodopa response is variable and transient in most reported cases. Non-invasive (continuous or nocturnal) or invasive supported ventilation can improve survival, though such measures are often poorly tolerated. Diaphragmatic pacing has been tried, discussed in a single case report in which a patient with ventilator-dependent respiratory failure was weaned from mechanical ventilation after insertion of the pacemaker, and remained stable at two year follow up [15].

Although Perry syndrome is rare, characteristic clinical features are usually present, and it should be considered when Parkinsonism is accompanied by significant weight loss, ventilatory dysfunction, or an autosomal dominant family history of Parkinsonism. Here we describe three unrelated cases from a small population-base, raising the possibility that it may be under-recognised, though the absence of pathogenic *DCTN1* mutations in the community-based CamPaIGN and PICNICS cohorts highlights their rarity in sporadic Parkinson's disease cases. As with other dominantly inherited adult-onset genetic conditions, appropriate genetic counselling is essential prior to undertaking genetic analysis, particularly when predictive testing in asymptomatic family members is considered. Early recognition is important, because although the prognosis is poor, appropriate respiratory assessment and ventilatory support can improve life expectancy.

Statements and Declarations

Competing interests:

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Consent to participate:

Informed consent was obtained from all individual participants included in the study

Consent to publish:

The participants have consented to the submission of the case report to the journal.

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