**Title: Neurological rarities, DCTN1-related Parkinson-plus disorder**

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**Abstract**

DCNT-1-related parkinson-plus disorder (DPPD), also known as Perry syndrome, is an autosomal dominant neurodegenerative disorder characterised by levodopa-resistant parkinsonism, weight loss, mood changes and central hypoventilation. Respiratory insufficiency is proposed to be the predominant cause of death. It has previously been described in 87 individuals from twenty families with a worldwide distribution. The genetic aetiology is a pathological mutation in DCTN1 (Dynactin-1); at the neuropathological level it has been identified as a distinct TDP-43 proteinopathy.

Despite progress in understanding the underlying pathology, the prognosis remains poor. Respiratory support has shown promising improvements in life expectancy but is dependent upon recognition. The rarity of this disorder and the clinical overlap with other neurodegenerative diseases increases the risk of delayed or misdiagnosis. We report a patient with DPPD, in whom genetic confirmation was not achieved until after death, as a means of increasing awareness of the disorder among neurologists.

**Introduction**

DCTN1-related parkinson-plus disorder (DPPD), also known as Perry syndrome, is an autosomal dominant neurodegenerative disorder first described by Perry et al in 1975 [1]. Onset of symptoms usually occurs in the fifth decade. The characteristic features are parkinsonism, weight loss, mood symptoms and progressive respiratory changes, principally tachypnoea and nocturnal hypoventilation, which emerges later in the disease course [1]. Polysomnography studies demonstrate cheyne-stokes respirations, periods of apnoea and fragmented sleep patterns. The majority of patients die as a result of respiratory failure or complications such as pneumonia [1]. Around 15% of all reported patients have died suddenly and it has been posited that apnoeic periods may be the cause [2].

The clinical syndrome can overlap with other neurodegenerative diseases such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) potentially leading to misdiagnosis [1]. Whilst a comprehensive review in 2008 identified 7 kindreds worldwide, more recent attempts to establish diagnostic criteria identified eighty-seven patients from twenty families [1].

The genetic aetiology of this disorder is a pathological mutation in exon 2 of the Dynactin-1 (DCTN1) gene which encodes part of the Dynactin complex [2]. Despite at least five distinct substitutions being identified, all cluster generally around the CAP-Gly domain of DCTN1. It has been identified at the neuropathological level as a TDP-43 proteinopathy with a distinctive pattern of disease predominantly localised to substantia nigra and globus pallidus with characteristic p50 neuronal cytoplasmic inclusions.

Despite advances in the understanding of this pathology, prognosis remains poor. The use of antidepressants to alleviate psychiatric symptoms is usually ineffectual [1, 2] and extrapyramidal features are usually only minimally responsive to levodopa. [1]. Respiratory insufficiency has been treated with non-invasive positive pressure ventilation and tracheostomies [1]. An alternative approach is the placement of bilateral diaphragmatic pacemakers, a technique initially developed for high cervical spinal cord injuries [1]. Diaphragm pacing is achieved through the stimulation of the phrenic nerve via electrodes placed through a small operation.

The potential benefits of respiratory support mean that life expectancy might be improved if the diagnosis is recognised. However, the rarity of the disorder and its clinical overlap with other neurodegenerative diseases increases the risk of misdiagnosis. In this case report we present a genetically confirmed case with a slightly atypical phenotype in whom the diagnosis was made only after whole genome sequencing as part of the 100,000 genomes project.

**Case Report**

In 2014, a 61-year-old right-handed woman presented to clinic with a two-year history of cognitive decline, weight loss and changes in gait and body movement. Her relatives stated that she had become ‘quieter’ in personality, apathetic and slow to move. She reported mild cognitive fluctuations, fatigue and a continuous feeling of nervousness but denied any visual hallucinations or sleep disturbance. Her father had developed atypical parkinsonism at 66. Examination showed a short stepping gait with almost no arm swing and significantly reduced postural reflexes. Hypophonia and facial passivity were present but there was no supranuclear gaze palsy. There was no rest tremor but a mild upper limb action and intention tremor was present bilaterally. Mild cogwheeling was present at both wrists. Upper limb reflexes were brisk, particularly in the left arm. Palmomental reflexes were present bilaterally. Her weight was 45.7kg. Previously undertaken cognitive testing demonstrated significant impairments in verbal and visual memory, processing speed and attention. Brain MRI was reported to be unremarkable. Cardiac MIBG was normal. A diagnosis of a neurodegenerative parkinsonian disorder was made, possibly evolving MSA. She was prescribed levodopa.

Over the next three months, her weight dropped to 44.1kg. Levodopa did not alleviate her symptoms and caused mild orofacial dyskinesias. Levodopa was withdrawn and Rivastigmine was introduced with some improvement in memory and other aspects of cognition. Throughout the following year, with interventions by dieticians, physiotherapy and occupational therapy, her weight stabilised and adaptions to her home environment were made. Unfortunately, her other symptoms progressed and within a year of initial presentation she had retired from work and become fully dependent on carers. Postural instability became a prominent issue with recurrent backwards falls, some resulting in hospital admission. Amantadine and Selegiline provided no symptomatic benefit. She experienced a single episode of visual hallucinosis and worsening of cognitive performance, especially working memory. Repeat brain MRI eighteen months later reported diffuse sulcal prominence greater than expected for age and reduced volume of basal ganglia which in retrospect was visible on the previous MRI. At this point, Levodopa was recommenced leading to an improvement in postural stability and fewer falls.

Three years from initial presentation she developed dysphagia, nocturnal cough and breathing difficulties. At rest, her breathing was shallow and panting. Intermittent periods of hyperventilation were witnessed in clinic. Her relatives described this as persistent throughout the day though settling at night, and denied ever witnessing any apnoeic periods.

Concurrent investigations into her father’s clinical history through retrospective examination of medical records revealed a similar presentation with weight loss and depression preceding treatment-resistant atypical parkinsonism. He had also developed impaired thermoregulation and flushing, often going outside in winter wearing few clothes as he felt ‘very hot’. He was admitted to hospital for assessment of respiratory changes and persistent tachypnoea. Shortly after this admission he died of a large vessel stroke at 69 years of age, four years after first experiencing symptoms.

Due to the history of atypical parkinsonism in a first degree relative, genetic studies were undertaken. No mutations were found in a panel of genes associated with Parkinson’s disease or similar disorders (genes in bold implicated in autosomal dominant parkinsonism: **AFG3L2**, ANO3, ATP1A3, ATP7B, CYP27A1, FA2H, **FTL**, **GBA**, **GCH1**, GNAL, **LRRK2**, **MAPT**, PANK2, PARK2, PARK7, PINK1, PNKD, PRKCG, PRRT2, SGCE, SLC16A2, SLC2A1, SNCA, SPG11, SPR, TH, TH81 and WDR45). At this point the patient consented to an analysis of her whole genome as part of the 100,000 genomes study. Shortly afterwards, five years after onset of symptoms and a period of deteriorating health due to recurrent urinary tract infections, she died as a result of respiratory insufficiency in her local hospital. After her death she was found to be heterozygous for a known pathogenic variant of the DCTN1 gene c.211G>A p. (Gly71Arg).

**Discussion**

This patient demonstrates the core phenotype of DPPD; parkinsonism with accompanying apathy and mood symptoms, weight loss and later respiratory problems. With a suggestive family history and a known pathological mutation, she fulfils the diagnostic criteria proposed by Mishima et al. [1]. However unlike the proposed criteria, the patient and her father first experienced symptoms in their late fifties or early sixties, a decade later than the average age of onset (41.9 years) [1]. The degree of cognitive decline experienced by our patient is unusual. Previously, mild cognitive impairment has only been reported in 10 patients [1], and visual hallucinations as experienced by our patient are uncommon, having only been described in two other individuals [1]. If we consider the patient’s father also suffered from this disorder, thermo-dysregulation of this extent has also not been previously documented.

Gly71Arg is the most common mutation, being identified in the original Canadian family, a number of other families in Turkey, Korea, Columbia and the USA and two unrelated families in the UK [2]. Even among patients with the same mutation there is moderate variation in initial symptoms and disease progression. This makes early recognition challenging, such that this diagnosis may only be considered with the onset of respiratory changes i.e. much later in the disease process. At this point sudden death or respiratory failure presents a real risk.

DPPD is known to have a highly variable and often transient response to levodopa. Other medications such as dopamine agonists, MAO-B inhibitors and cholinesterase inhibitors also have limited benefit [1]. As in this case, physiotherapy, occupational therapy and speech and language teams can assist in sustaining quality of life. Unfortunately, none of these interventions address the primary cause of mortality, respiratory insufficiency. Whilst continuous or nocturnal non-invasive BiPAP or invasive ventilation strategies such as intubation or tracheostomy [1] have been implemented with the prolonging of life these are not without risk and often poorly tolerated. In the single case report of diaphragmatic pacing, the patient was weaned off invasive ventilation and was still living independently two and a half years later [1].

We agree with other authors who propose that DPPD should be considered in any patient with atypical parkinsonism, especially where weight loss and mood changes are prominent early features, irrespective of whether changes in respiration are seen at initial presentation. Through this approach we may achieve earlier diagnosis of the disorder. This will enable better informed conversations with patients, access to (or research into) respiratory interventions and genetic counselling for family members.

**Key Points**

1. DCNT-1 related parkinson-plus disorder (DPPD) is an autosomal dominant parkinsonism caused by a mutation in the Dynactin-1 gene.
2. DPPD should be considered as a differential in atypical parkinsonism, especially where weight loss and mood changes are also present.
3. Central hypoventilation is a cardinal feature of late disease and major cause of death.
4. Early diagnosis and effective treatment have been shown to prolong life and improve life quality.

**References**

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**Competing interests**

There are no competing interests for any author.

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DR undertook the literature review and write up of the article under the supervision of JDI. ME provided specialist input and contributed to the write up of the article. All authors read and approved the final manuscript.

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**Data sharing statement**

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.