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Short communication

Parkinsonism in PGK1 deficiency implicates the glycolytic pathway in nigrostriatal dysfunction

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ABSTRACT

Background: Phosphoglycerate kinase-1 deficiency is caused by X-linked recessive mutations in *PGK-1* and associated with haemolytic anaemia, rhabdomyolysis, myopathy and nervous system involvement. Some cases have been rarely associated with juvenile Parkinsonism however the causal relationship between PGK1 deficiency and nigrostriatal dysfunction causing Parkinsonism has not been determined.

Objective and methods: To investigate the nigrostriatal system using 99mTc-TRODAT-1 SPECT binding and report the phenotype of three affected males with early onset levodopa responsive Parkinsonism harbouring the c.491 A > T/p.D164V pathogenic variant.

Results: All patients initially presented with infantile-onset encephalopathic and stroke-like episodes, haemolytic anaemia and epilepsy. Two patients had an early-onset and one juvenile-onset levodopa responsive Parkinsonism with motor fluctuations. 99mTc-TRODAT-1 SPECT showed severe bilateral reduced putaminal uptake in the three patients. None of the patients had structural lesions that could explain either pre- or post-synaptic dopaminergic dysfunction.

Conclusion: These cases provide strong evidence of a causal relationship between PGK1 deficiency and nigrostriatal pathology causing Parkinsonism. These findings have potential implications for our understanding of the pathophysiology of nigrostriatal degeneration in sporadic PD.

1. Introduction

Phosphoglycerate kinase-1 (PGK1) deficiency is caused by X-linked recessive mutations in *PGK-1* and associated with a combination of clinical manifestations including haemolytic anaemia, rhabdomyolysis, myoglobinuria, myopathy and nervous system involvement [1,2]. Frequent neurological syndromes include intellectual disability, stroke-like episodes and epilepsy. Around 50 cases with PGK1 deficiency have been described in the literature; however, Parkinsonism has been reported only in four kindred [2–7]. We report a two-generation family with the c.491 A > T pathogenic variant in *PGK-1* with three affected males from three different trios showing early onset levodopa responsive Parkinsonism and reduced putaminal Tc-99 m TRODAT SPECT binding. These cases strengthen the association between PGK1 deficiency and Parkinsonism and suggest a causal relationship between impaired energy metabolism and nigrostriatal dysfunction.

2. Methods

The study protocol was approved by the Local Research Committee (HREC2014/2/5.3), and all patients consented for the study. The family was diagnosed with PGK deficiency in the context of haemolytic anaemia in one of the offspring that died in the neonatal period (Index case, Fig. 1). Molecular confirmation in the index patient revealed the previously reported c.491 A > T/p.D164V pathogenic variant, and it was further confirmed in the carriers and affected male patients. Female carriers in the family have no reported neurological abnormalities. Tc-99 m TRODAT SPECT was performed in the three affected patients. The family has been the subject of an earlier report, prior to Parkinsonism manifesting in any of its members [1]. Signed consent for online

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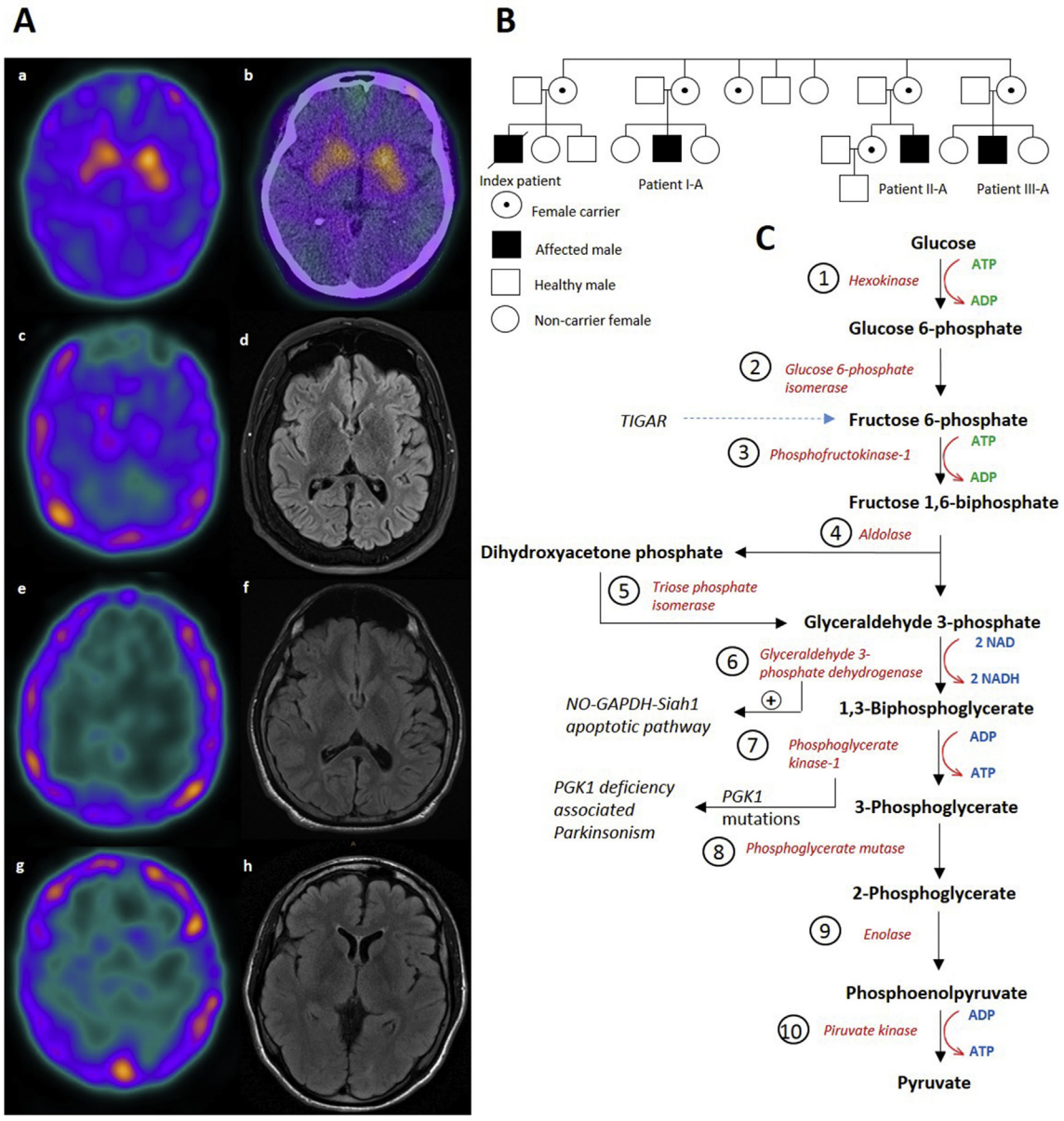

Fig. 1. Tc-99 m TRODAT SPECT in PGK1 deficiency and glycolysis pathway (for color online)
The left (A) panel shows a normal brain Tc-99 m TRODAT SPECT (a) and fused CT scan (b) for comparison. The Tc-99 m TRODAT SPECT scan of patient I-A shows severely diminished with increased unspecific tracer binding (c). Patient II-A demonstrated had a severely reduced bilateral striatal uptake (e) whereas patient III-A had an asymmetrically but severely diminished striatal uptake (g). MRI brain of the three patients did not have basal ganglia or subcortical lesions (d, f, h). Panel B describes the family tree of the kindred affected with PGK1 deficiency with the c.491 A > T mutation. The right (C) panel shows a simplified version of the glycolytic pathway. Glycolysis converts glucose to pyruvate thought ten different catalytic reactions generation ATP and NADH in the process. TIGAR (TP53-Induced Glycolysis and Apoptosis Regulator) decrease levels of Fructose 6-Biphosphate the substrate of Phosphofructokinase-1, the key enzyme in the glycolytic pathway. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activates the NO-GAPDH-Siah1 apoptotic pathway (not shown), and overexpression has been found in SN of PD patients. Phosphoglycerate kinase-1 generates ATP during the conversion of 1,3-diphosphoglycerate to 3-phosphoglycerate. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

publication and dissemination of all persons visible on the videos were obtained for this study.

3. Results

Patient I-A was born from a healthy pregnancy without neonatal complications. At the age of 12 months, he developed recurrent generalised seizures that were controlled with carbamazepine. He then had a spontaneous stroke-like episode with coma at the age of 18 months, which left him with a mild left hemiparesis. He was also diagnosed with haemolytic anaemia. At the age of 9 years, he had a second episode with cerebral oedema requiring mechanical ventilation for six weeks. After this episode, he recovered his motor function over one year. At the age of 30 years, he noticed a postural tremor affecting both upper limbs and slowness of hand movements. Examination at age 33, revealed a short stature and moderate intellectual disability. He had hypomimia, hypophonia, with asymmetric moderate bradykinesia on finger tapping and transient pronation-supination right rest arm tremor, mild bilateral postural tremor and mild right arm rigidity (MDS-UPDRS Part III, 50 points) (Supplementary video 1). Also, there was a mild generalised muscle weakness with normal reflexes and flexor plantar reflexes. An ophthalmological evaluation revealed the presence of retinal

Table 1
Clinical, imaging and molecular characteristics of patients with PGK1 deficiency and Parkinsonism.

	Patient I-A (This report)	Patient II-A (This report)	Patient III-A (This report)	Virmani T et al. [6,7]	Virmani T et al. [6]	Sakaue et al. [8]	Konrad et al. [2]	Konrad et al. [2]
Gender	Male	Male	Male	Male	Male	Male	Male	Male
PGK1 deficiency symptoms	Haemolytic anaemia at 18 months	Jaundice at 12 months	Haemolytic anaemia at age 42	Childhood-onset progressive weakness and muscle atrophy and myoglobinuria	Weakness and exercise-induced rhabdomyolysis at age 7 years	Haemolytic anaemia and myoglobinuria at age 3 years	Neonatal jaundice	Neonatal jaundice
Age at first neurological symptoms	Seizures at 12 months	Acute encephalopathy at 2 years	Stroke-like episodes at 5 years	Childhood-onset exercise intolerance, myalgia and myoglobinuria	Progressive weakness and exercise-induced rhabdomyolysis at age 7 years	Tremor at age 9 years	Tremor at age 12 years	Tremor at age 9 years
Age at last examination	34 years	32 years	42 years	30 years	24 years	16 years	19 years	17 years
Cognitive developmental milestones	Moderately delayed at age 2	Mildly delayed	Mildly delayed	Delayed	Normal	Delayed	Delayed at age 3 years	Delayed at age 3 years
Epilepsy	+	+	+	Not reported	No reported	–	–	–
Encephalopathic episodes	+	+	–	Not reported	No reported	Not reported	Not reported	Not reported
Stroke-like episodes	+	+	+	Not reported	Not reported	Not reported	Not reported	Not reported
Muscular symptoms	–	–	–	+, exercise-induced rhabdomyolysis	+, exercise-induced rhabdomyolysis	Not reported	Not reported	Not reported
Haematological manifestations	Haemolytic anaemia and myoglobinuria	–	Haemolytic anaemia and myoglobinuria	–	–	Haemolytic anaemia and myoglobinuria	Haemolytic anaemia and myoglobinuria	Haemolytic anaemia and myoglobinuria
Rest tremor	+	+	+	+	+	+	+	+
Bradykinesia	+	+	+	+	+	+	+	+
Rigidity	+	+	+	+	+	+	–	+
Dystonia		+, upper and lower limbs					+, upper limbs and lower limbs	+, yes upper limbs and lower limbs
Postural instability	–	+	+	+	+	+	Not reported	Not reported
Pyramidal signs	–	–	–	NR	Not reported	Not reported	–	–
Cerebellar signs	–	–	–	–	No reported	Not reported	–	–
Levodopa response	Moderate	Moderate	Moderate	Good	Moderate	Mild	No improvement	No improvement
Levodopa-induced dyskinesias		+, mild to moderate	–	Not reported	+	Not reported	–	–
Behavioural abnormalities		Psychosis at age 15 years	–	Hallucinations and frontal-behaviour induced by levodopa	Aggressive and irrational behaviour induced by levodopa	Not reported	Not reported	Not reported
Abnormal cognition	+	+	+	+	–	Not reported	+	+
Myopathic signs	Mild upper limb weakness	_	–	mild lower limb weakness	Not reported	Not reported	–	–
Autonomic symptoms	–	Faecal and urinary incontinence	–	Faecal and urinary incontinence	Not reported	Faecal and urinary incontinence	Not reported	Not reported
MRI brain	Normal at age 34 years	Normal at age 28 years	Normal at age 40 years	Normal	Not reported	Mild atrophy of cerebellum and basis pontis	Not reported	Not reported
Nigrostriatal imaging	TRODAT scan bilateral moderate reduction striatal binding	TRODAT scan at age 32 years, bilateral severe reduction striatal binding	TRODAT scan at age 40 years, bilateral moderate reduction striatal binding	Not reported	Not reported	Marked bilateral reduction DAT scan binding	Not reported	Not reported
Amino acid change	p.D164V	p.D164V	p.D164V	p.T378P	p.T378P	p.A354P	Not reported	Not reported
Nucleotide change	c.491 A>T	c.491 A>T	c.491 A>T	c.1132 A>C	c.1132 A>C	c.1060 G>C	Not reported	Not reported
RBC residual PGK1 activity [4]	5%	5%	5%	2%	2%	6%	3%	2%

Abbreviations: NA: not available; RBC: red blood cells; +: present; -: absent.

dystrophy. The rest of the examination including cranial, eye movements, sensory and cerebellar examination was normal. He reported a 50–75% improvement of his tremor and bradykinesia with rasagiline and levodopa. MRI brain at age 34 showed no focal basal ganglia or cortical pathology. Tc-99 m TRODAT SPECT scan showed bilateral reduced putaminal uptake (Fig. 1A).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.04.004

Patient II-A was a product of normal pregnancy but was born jaundiced and had his first episode of haemolysis before age 1. He had three encephalopathic episodes between age 2 and six years, characterised by seizures and coma from which he recovered gradually and developed epilepsy that was controlled with phenytoin. At the age of 13, he had a stroke-like episode with right-sided paralysis which recovered spontaneously over days. He developed psychotic symptoms at the age of 15 and was started on antipsychotics starting with thioridazine. Then he gradually developed right arm dystonia with elevation of the shoulder at the age of 17 years however over one week he developed severe slowness of movement and urinary and faecal incontinence. Although after switching to olanzapine his symptoms improved moderately he later developed a gradual decline in motor function being unable to walk unassisted and progressive dysphagia. On examination at age 27, he had hypomimia, severe hypophonia, asymmetrical rest tremor more in the right arm and leg, moderate to severe akinesia and moderate rigidity more in the lower limbs (Supplementary video 2). There were no eye movement abnormalities, cerebellar, sensory or pyramidal signs. Treatment with levodopa improved his overall mobility partially being able to walk. At age 31 he developed severe motor fluctuations which were managed successfully with levodopa/carbidopa intestinal gel, although his mobility continued to decline. MRI brain at age 28 years was normal. Tc-99 m TRODAT SPECT scan showed asymmetrical putaminal uptake reduction (Fig. 1A).

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Patient III-A, the product of normal birth and early motor development, developed stroke-like episodes with severe right-sided paralysis resolving in weeks at the ages of 5 and 7. Brain MRI in one of the episodes was reported abnormal but the abnormalities resolved after the attack. At age ten he started treatment with carbamazepine for epilepsy and at the age of 36, he noticed a left arm rest tremor without impartment of fine motor control. Examination at age 38 years, he had mild intellectual disability, asymmetrical pronation-supination rest tremor and mild postural and intention tremor. Mild bradykinesia during finger taps on the left hand, mild rigidity with reduced left-arm swing was also noted (Supplementary video 3). There was no bradykinesia or rigidity in the lower limbs. The rest of the examination was unremarkable. He had moderate improvement of the tremor with levodopa. At age 42 he had a flu-like illness associated with haemolytic anaemia and haematuria that required blood transfusions. MRI brain at age 40 was unremarkable. Tc-99 m TRODAT SPECT scan showed bilateral reduced putaminal uptake (Fig. 1A).

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None of the patients had symptoms suggestive of REM sleep behaviour disorder before or after Parkinsonism. However, we did not performed polysomnography or cardiac MBIG in any of our patients.

4. Discussion

We report a family with PGK1 deficiency and associated young or juvenile onset, levodopa-responsive Parkinsonism with nigrostriatal dysfunction demonstrated by functional dopaminergic imaging. Our patients had the previously reported c.491 A > T pathogenic variant and initially presented with infantile-onset encephalopathic and stroke-like episodes, haemolytic anaemia and epilepsy. In addition, they featured intellectual disability, as has been reported in previous cases. Importantly, none of the patients had structural lesions that could explain either pre- or postsynaptic dopaminergic dysfunction.

Parkinsonism in PGK1 deficiency has been reported in two patients with the c.1132 A>C and one with the c.1060 G>C mutation, all of which presented with haemolytic anaemia, exercise intolerance and rhabdomyolysis in early childhood and subsequently Parkinsonism at age 19, 10 and 9, respectively [5,6]. Juvenile-onset dystonia-parkinsonism with leukodystrophy has been reported in a patient also with the c.1060 G>C mutation [8]. Moreover, Konrad, et al. reported two siblings, in whom PGK1 deficiency was diagnosed by enzyme analysis, who also presented with intellectual disability, haemolytic anaemia and juvenile onset Parkinsonism [2] (Table 1). While these cases suggest the possibility that juvenile onset Parkinsonism may be a manifestation of PGK1 deficiency, its absence in the vast majority of patients means that a coincidental genetic or other cause has not been able to be excluded; although unlikely, the co-occurrence of rare recessive disorders has been reported in occasional kindred. Other X-linked early onset Parkinson's disease mutations such as RAB39B and ATP6AP2 were not tested in our patients; however these disorders have been associated with other specific manifestations such as basal ganglia calcification and spasticity that were not present in our patients [9,10]. The occurrence of a Parkinsonian phenotype in our three patients, all with different parents including unrelated fathers, makes a coincidental coexistent rare genetic cause of Parkinsonism extremely unlikely and provides strong evidence of a causal relationship between PGK1 deficiency and nigrostriatal pathology causing Parkinsonism.

Ten different enzymes orchestrate glycolysis and PGK1, in particular, generates ATP in the process through the conversion of 1, 3-diphosphoglycerate to 3-phosphoglycerate (Fig. 1B). In patients with PGK1 deficiency, it is recognised that the level of residual enzymatic activity may influence the phenotype, where low glycolytic activity (red blood cell PGK1 activity < 3%) results in a multisystemic disorder [3]. The c.491 A > T mutation reduces catalytic activity and protein stability of PGK1, and it is associated with a residual function of 5% in red blood cells, whereas the c.1132 A>C and c.1060 G>C mutation have a 2% and 6% residual activity, respectively [4]. The mechanisms underlying neuronal damage in PGK1 deficiency are unknown however it has been speculated that neuronal damage occurs as a consequence of energy failure. To date, only two other abnormalities in the glycolytic pathway have been implicated in the pathogenesis of nigral damage in Parkinson's disease (PD). Specifically, overexpression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a glycolytic enzyme that converts D-glyceraldehyde-3-phosphate into 1, 3-diphosphoglycerate, has been found in cytoplasmic Lewy bodies in the substantia nigra of PD patients and in nigral neurons of PD animal models [11]. GAPDH overexpression can activate the NO-GAPDH-Siah1 apoptotic pathway and interestingly, selegiline and rasagiline bind to GAPDH preventing nuclear translocation and subsequently cell death [12]. In addition, the *T*P53-*I*nduced *G*lycolysis and *A*poptosis *R*egulator (TIGAR) is an inhibitor of glycolysis, and its upregulation in *PINK1* mutations causes mitochondrial dysfunction and selective nigral damage [13]. Furthermore, TIGAR is detected in subtantia nigra Lewy bodies of sporadic PD patients suggesting a role in glycolysis in the pathogenesis of nigral damage [14].

In conclusion, our patients strengthen the causal link between PGK1 deficiency and nigrostriatal dysfunction and have potential implications for our understanding of the pathophysiology of sporadic PD. The glycolytic pathway has received relatively little attention as a potential pathogenic mechanism in PD. Furthermore, PGK1 deficiency should be considered in the differential diagnosis of juvenile or early onset Parkinsonism in particular in patients with haemolytic anaemia, myopathy, epilepsy and intellectual disability.

Author contributions

Conception and study design (HM, AH, VF), data acquisition (HM,

AH, KL, DF, FC, VF), drafting first version of the manuscript (HM, AH), figures and tables (HM, AH, KL), final version of the manuscript (HM, AH, KL, DF, FC, VF). Study supervision (VF).

Potential conflict of interest

None.

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