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CASE REPORT

A rare co-occurrence of phosphorylase kinase deficiency (GSD type IXd) and alpha-glycosidase deficiency (GSD Type II) in a 53-year-old man presenting with an atypical glycogen storage disease phenotype

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Glycogen Storage Disease (GSD) IXd, caused by *PHKA1* gene mutations, is an X-linked rare disorder that can be asymptomatic or associated with exercise intolerance. GSD type II is an autosomal recessive disorder caused by mutations in the *GAA* gene that lead to severe cardiac and skeletal muscle myopathy.
We report the first case of co-occurrence of type IXd and type II GSDs in a 53-year-old man with an atypical glycogen storage disease presentation consisting in myalgia in the lower limbs at both rest and after exercise and increased levels of transaminases from the age of 16. At the age of 43, the patient presented a steppage gait, inability to run and walk on his heels, hypotrophy of the pectoral and proximal muscles, reflexes not elicitable, and CK levels 3.6 times the upper reference limit. Next Generation Sequencing (NGS) identified one variant in the *PHKA1* gene, c.1360A > G p.Ile454Val (exon 14) inherited by his mother, and two heterozygous variants in the *GAA* gene, c.784G > A (exon 4) and c.956-6T > C (exon 6). A review of GSD IXd cases reported to date in the literature is also provided.

Key words: Phosphorylase kinase deficiency, GSD type IXd, alpha-glycosidase deficiency, GSD type II, co-occurrence

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Introduction

Glycogen storage diseases (GSDs, glycogenoses) are a group of genetic disorders resulting from abnormal metabolism of glycogen, a polymeric molecule involved in glucose storage [1-3]. Currently thirteen different types of glycogenosis are known. They all result from mutations in genes for different enzymes, which directly or indirectly regulate glycogen synthesis and/or degradation. The overall GSD incidence is estimated to be 1:20000-43000 live births. The histopathological hallmark is muscle fibres vacuolization and auto-

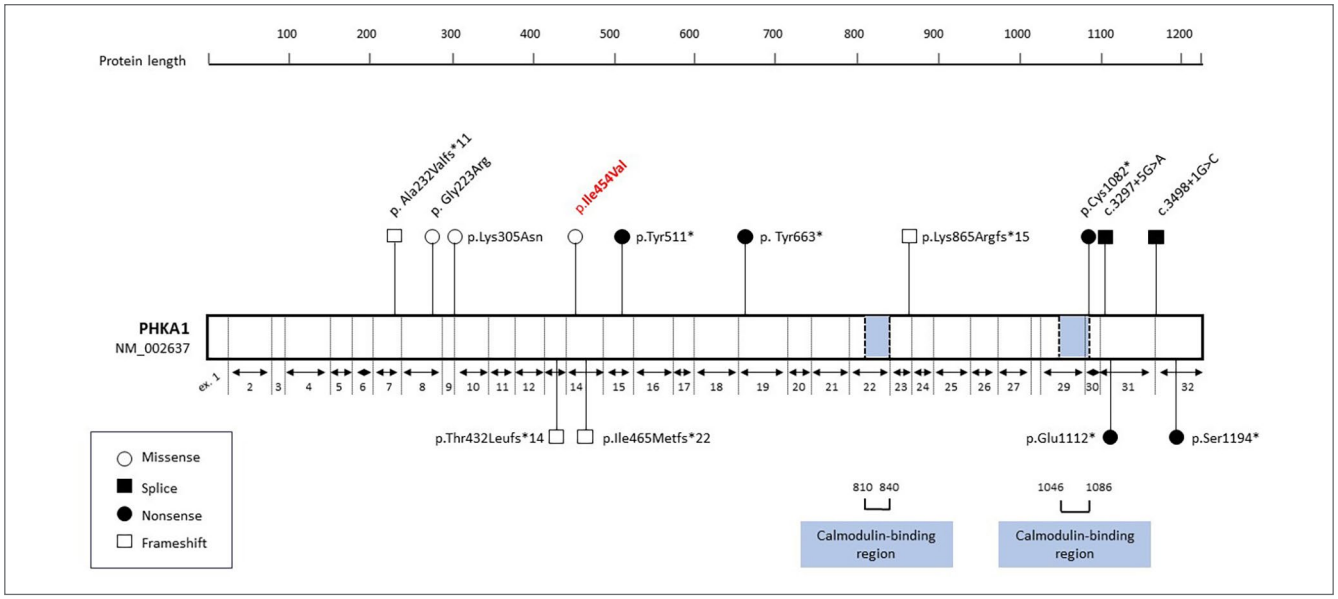

Figure 1. Graphical view of PHKA1 protein. Calmodulin-binding regions are coloured in sky blue. The nonsense, missense, frameshift and splicing pathogenic variants so far described are reported using different symbols and grouped according to their effect. The variant identified in our patient is highlighted in bold red.

phagy. The vacuoles that show marked PAS-positivity can vary greatly in size and shape [1-4]. However, they are not always detectable on muscle biopsy.

Diagnosis is usually based on clinical manifestations and laboratory test results but molecular analysis is often necessary to distinguish the various types, which may share a similar presentation [2-4].

Disorders of glycogen degradation may affect primarily liver, muscle, or both. Spectrum and severity of symptoms depend on the type and subtype of the disease as well as on the individual characteristics [2-4].

Type II GSD or Pompe disease is a prototype of inborn lysosomal storage diseases, caused by the deficiency of the lysosomal enzyme acid α-glucosidase (GAA) [4]. The disease is inherited with an autosomal recessive pattern, involves many organs but primarily affects muscles. The enzyme deficiency leads to lysosomal glycogen accumulation and results in two main different clinical phenotypes (severe or infantile, juvenile and/or adult onset). The infantile form of GSD type II, named early-onset Pompe disease (EOPD), usually due to complete GAA deficiency, is characterised by marked hypotonia and cardiomyopathy; patients die within the first year of life, if untreated, for cardio-respiratory failure [5].

The juvenile and/or adult forms, named late-onset Pompe disease (LOPD), are slowly progressive myopathies often mimicking limb-girdle muscular dystrophy. The milder phenotype is likely due to residual enzyme activity. However, an early respiratory involvement with a restrictive pattern is of frequent observation while heart is usually spared [6]. Enzyme replacement therapy is currently available for this type of glycogenosis [7].

GSD type IXd is a very rare X-linked glycogenosis primary affecting liver. The disease starts generally in adolescence or adulthood. Hypoglycaemia and hepatomegaly are hallmarks of the liver disease, but muscle and renal tubular involvement, dyslipidaemia and osteopenia can also develop [8,9]. Patients may present exercise intolerance with myalgia, cramps, fatigue, and sometimes myoglobinuria. In some cases, patients may have progressive muscle weakness. Symptoms are usually mild in late onset disease, and myopathy may be asymptomatic.

Cases with prevalent muscle involvement are caused by mutations in *PHKA1* gene. There are very few cases of isolated GSD IXd [8-18] described in the literature (Fig. 1), and only one in association with non-dystrophic myotonia [13].

We herein report an unusual case of co-occurrence of type IXd and type II GSD in a 53-year-old patient with an atypical glycogen storage disease presentation, consisting in myalgia in the lower limbs at both rest and after exercise and increased levels of transaminases from the age of 16, associated to neuropathic aspects.

Furthermore, we provide a review of GSD IXd cases reported to date in the literature and comparing their clinical and genetic results with those observed in our patient.

Patient's description

A 43-year-old man was admitted to the Cardiomyology and Medical Genetics Service of the Second Naples University Hospital, for difficulty in walking uphill, especially with the right limb. Parents were not consanguineous. He is the first of four children, three boys and one girl. Of note are several cases of sudden cardiac death in the mother's family (grandfather, two uncles and an aunt). One brother presented mild elevation of Creatine Kinase (CK) after exercise. The patient was born at full-term from spontaneous delivery. He began to complain of myalgia, both at rest and after exercise, at the age of 16. An orthopaedic specialist consulted at that time attributed the symptoms to bilateral pes cavus and prescribed orthotics, without obtain-

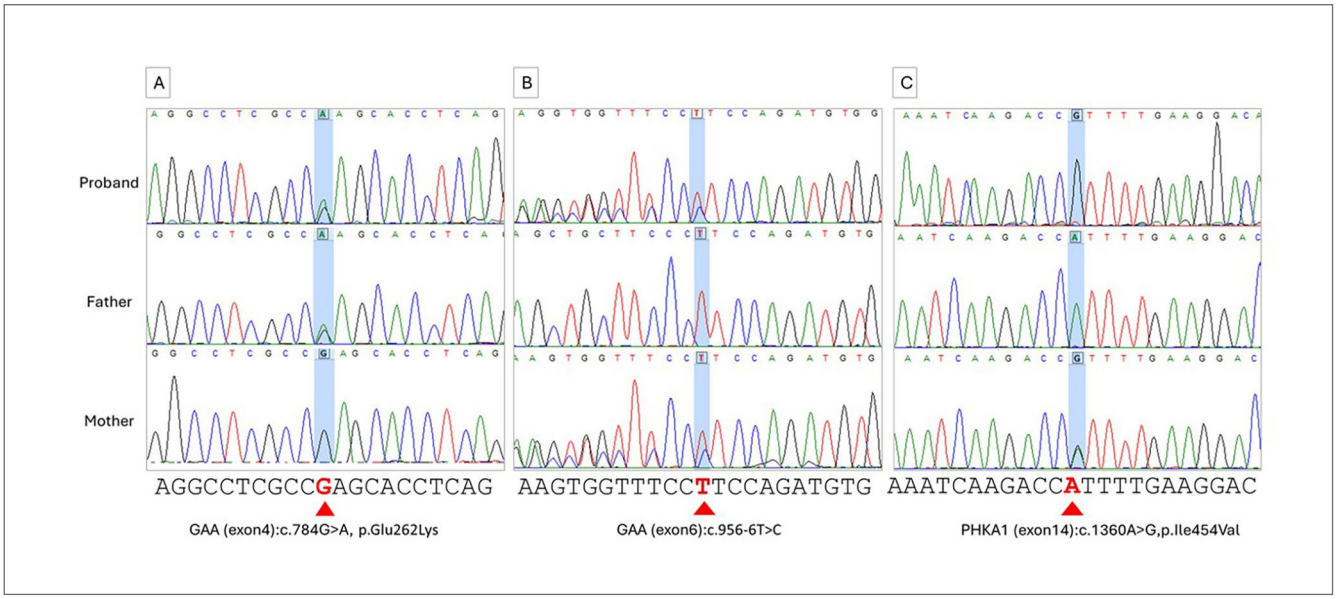

Figure 2. Electropherograms of the *GAA* and *PHKA1* genes. In panel A and B, the electropherograms confirm the compound heterozygous missense mutations (c.784G>A and c.956-6T) in the *GAA* gene identified in the proband and inherited from the father and mother, respectively. In panel C, electropherograms confirm the missense mutation (c.1360 A>G) in the *PHKA1* gene identified in the proband (hemizygous) and in the mother (heterozygous).

ing any benefit. Two electro-neuro-myographic tests, performed at different periods, given conflicting results. The first ENMG, performed when he was 21 years old, showed not clear signs of pathology due to the simultaneous presence of primary and secondary damage in muscles explored. Repetitive stimulation and motor and sensory conduction in the tibialis posterior muscle were normal, with the exception of a discrete reduction in the distal section.

Muscle needle biopsy performed at the same age showed fair variation in fibre size with splitting phenomena, increased number of nuclei, increased number of type I fibres, and a mild increase in endoperimysial connective tissue. There was accumulation of oil-red-positive material in some fibre groups while the glycogen content was normal. The diagnosis was*: "Clear signs of neurogenic muscle damage; the presence at the same time of myopathic aspects, and the number of fibres involved in the formation of type grouping (at the basis of neurogenicity) indicate the non-recent date of the pathogenetic input".*

A sural nerve biopsy was also performed which showed absence of onion bulbs, inflammatory infiltrates and accumulation phenomena.

An EMG, performed 10 years later, showed findings compatible with moderate aspects of muscular damage in the explored muscles of the lower limbs such as left quadriceps femoris, right tibialis anterior and left surae.

When he came under our observation, the patient reported that muscle symptoms had been slowly progressive, not limiting his daily activities. However, a clear worsening had occurred in the previous 3-4 years, with increasing difficulty in going up and down the stairs with the need to support the handrail, and difficulty in walking uphill, prevalent on the right.

On physical examination, he showed stepping gait to the right, difficulty in rising from the floor and in rising stairs, inability to run and walk on his heels, hypotrophy of the pectoral and proximal muscles, winging scapula, non-elicitable reflexes. The assessment of muscle function showed 4-MRC-scale score at the upper limbs, and 14/34 North Star Ambulatory Assessment (NSAA) score. CK values were 3.6 times the upper reference limit, while transaminases were only slightly elevated. Standard ECG and echocardiography were normal. Spyrometric parameters such as FVC, PEF and FEV1 were within the normal limits.

More recently, the genetic re-evaluation of the unsolved cases by NGS analysis identified one variant in the *PHKA1* gene, c.1360A > G p.Ile454Val (exon 14), inherited by his mother and two heterozygous variants in the *GAA* gene, c.784G > A (exon 4), and c.956-6T > C (exon 6) confirmed by sequencing Sanger (Fig. 2).

At the last visit, about six months ago, the patient was able to take only a few steps independently, with a stepping gait to the right, but he was unable to get up from the floor and go up/down stairs. Postural transitions (from supine position to sitting or from sitting position to standing) were possible only with compensatory maneuvers. Muscle examination showed proximal hypotrophy of the lower limbs; hypotrophy of the glutei, brachial biceps and pectoral muscles, winging scapula. Lumbar hyperlordosis, right dorsal and left lumbar scoliosis, and tibio-tarsal contractures were also present.

The FVC values were 92% in sitting position and 88% in supine position. Cardiological parameteres were within the normal limits.

Discussion

GSD type IXd is a very rare metabolic myopathy with a benign phenotype. To date, only 14 cases are reported in the literature (Tab. I). Their main presenting symptoms are muscle weakness in lower limbs (48.2% of patients) and exercise intolerance and/or myalgia (57.1%). Other symptoms such as muscle stiffness, difficulty with climbing stairs, cognitive impairment and increased CK levels occur

Table I. Clinical and genetic characteristics of patients with PHKA1 pathogenic variations so far reported in literature.

Patient's ID	Age at presentation (years)	Presenting symptoms and signs	CK values	*PHKA1* nucleotide change
	16	**Myalgia, both at rest and after exercise**	**3.6X**	**c.1360A > G *GAA*: c.784G > A; c.956-6T > C**
01	46	Distal muscle weakness	?	c. 3334G > T
02	15	Premature fatigue and myalgia after intense exercise	3X	c. 3498+1G > C
03	50	Progressive exercise intolerance; muscle stiffness	2X	c. 831G > A
04	17	No exercise intolerance, nor stiffness; cognitive impairment	5X	c. 1394delT
05	69	Raised levels of creatine kinase (CK)	5X	c. 695delC
06	39	Exercise intolerance	195 -332 U/L	c. 1293delT
07	15	Muscle weakness in the lower limbs and upper limbs	464-2842U/L	c. 3246T > A ***KCNJ2***: c. 899G > C
08	40	Exercice intolerance, myalgia, cramps, progressive weakness; cognitive impairment	20.4X	c. 2594delA
09	16	Myalgia; exercise intolerance; pigmenturia	5-40X	c. 3579_3580insT
10	66	Progressive muscle weakness, dysarthria, chewing and swallowing difficulties; myopathic face	Normal	c.1989_1990delinsAAGTTGCTCGTGATCTAAA
11	41	Gradual muscle weakness and myalgia	55X	c. 1533T > A
12	31	Muscle weakness of the lower limbs	29.7X	c. 3297 + 5G > A
13	13	Swelling of the lower limbs associated with muscle weakness	2X	c.3670_3924del ***MT-TL1***: m.3243A > G
14	71	Difficulty with climbing stairs	1.05X	c.915A > T

Legenda: CK values are expressed as a number of times the maximum reference limit, when indicated.

in percentages varying from 7.1 to 14.2 of cases. The mean age of onset of symptoms was 36.3 ±20.9 years (range 13-71). In three patients, the onset of symptoms occurred between the sixth and seventh decade. Data on respiratory involvement is available in only two cases, one of them showing respiratory failure and the other normal spirometric values. Likewise, data on cardiac involvement is available in only three cases, the first presenting ECG abnormalities (positive U waves), the second reporting previous chest pain, and the third no heart involvement. There is variability in CK values, which range from normal values to 55 times the upper reference limit. The presence of PAS-positive vacuoles with glycogen accumulation was observed in 11/13 patients (84.6%) undergoing muscle biopsy. Two patients, both with late onset disease, had no vacuoles on muscle biopsy. The majority of variations were nonsense or frameshift variations (Tab. I). Only one case of co-occurrence of *PHKA1* variation with variation in another gene is described in a young man suffering from Andersen-Tawil syndrome and recurrent episodes of paralysis and muscle weakness [13].

In this report, we describe the fifteen case of GSD type IXd (Tab. I) in a patient with myalgia at rest and after exercise since the age of 16, associated to slight increase in transaminases.

Clinical presentation and instrumental investigation were atypical for a glycogen storage disease. Two electro-neuro-myographic tests had shown contrasting signs of neurogenic myopathy and primary myopathy while, at the muscle needle biopsy, no vacuoles and accumulation of glycogen were found as would be expected in the case of glycogenosis. The patient was offered a new open biopsy to better define the clinical picture, but he refused to perform it. However, it should be noted that muscle needle biopsy has been done more than 30 years earlier, and that the absence of vacuoles with glycogen accumulation is not rare in patients with LGSD type IXd [12] and LOPD [19,20].

The severity of the muscle phenotype observed in our patient is in contrast with the clinical picture of GSD type IXd as the latter usually has a relatively benign course, and may even be asymptomatic. By contrast, the absence of cardiac and respiratory involvement is consistent with GSD type IXd phenotype. The variation in *PHKA1* gene was inherited from the mother, who is 70 year old and affected by arterial hypertension, diabetes and dyslipidaemia. The brothers refused to perform genetic analysis. The atypical phenotype might be explained by the fact that the patient also presents compound heterozygous variations in *GAA* gene, inherited from his parents (Fig. 2). The variant c.784G > A in exon 4 is reported in ClinVar as pathogenic (VCV000188806.19), and it was described in 18 patients (https://www.pompevariantdatabase.nl); in 14/18 (77.8%) cases, it was associated with the classic infantile phenotype and in four (22.2%) with

PHKA1 aminoacid change	Muscle Biopsy	Cardiac Involvement	Respiratory involvement	Reference
p. Ile454Val	Normal glycogen content	NO	NO	Present case
p.Glu1112*	Focal glycogen excess	n.r.	n.r.	[8]
p. (?)	Accumulation of free glycogen at the periphery of some fibers	n.r.	n.r.	[9]
p. Gly223Arg	Elevated glycogen content	n.r.	n.r.	[10]
p. Ile465Metfs*22	Sub-sarcolemmal accumulation of free glycogen	n.r.	n.r.	[11]
p. Ala232Valfs*11	No vacuoles	n.r.	n.r.	[12]
p. Thr432Leufs*14	No vacuoles	n.r.	n.r.	[12]
p.Cys1082*	Subsarcolemmal vacuoles with glycogen storage	Prominent U waves at the ECG	n.r.	[13]
p. Lys865Argfs*15	Extensive subsarcolemmal vacuoles containing PAS-positive material	n.r.	n.r.	[14]
p.Ser1194*	Subsarcolemmal vacuoles in some myofibers	n.r.	n.r.	[15]
p. Tyr663*	n. p.	n.r.	Respiratory failure	[16]
p. Tyr511*	subsarcolemmal accumulation of glycogen	Chest distress one year earlier	n.r.	[17]
p. (?)	Subsarcolemmal accumulation of glycogen	n.r.	n.r..	[17]
Skip exons 29 and 30	Subsarcolemmal accumulation of glycogen	n.r.	n.r.	[17]
p.Lys305Asn	Vacuolar changes with glycogen accumulation	NO	NO	[18]

onset in childhood-adulthood. In the latter patients, the mutation was associated with the common variation c.-32-13T > G on the second allele. All of them had a benign evolution. The variant in exon 6, in accordance with Varsome and the ACMG guidelines, is to date classified as VUS (variant of uncertain significance).

By contrast the absence of respiratory involvement and the presence of stepping gait are atypical features of type II GSD. However, the presence of peripheral neuropathy has recently been reported in patients with late-onset type II GSD [21].

In conclusion, this is at our knowledge the first case of co-occurrence of two different types of glycogenosis. Therefore, it is difficult to establish how the presence of variations in multiple genes affecting muscle glycogen metabolism, have reciprocally influenced the course of the disease in our patients, as well as to establish how much of the phenotype can be related to one or to the other metabolic defect, or rather be the result of their interaction.

Conflicts of interest statement

The authors declare no conflict of interest.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and principles of Good Clinical Practice.

Informed Consent Statement

Informed consent for data collection and publication for research purposes, was obtained by the patient in the occasion of the blood collection for the genetic test as a consolidated hospital practice.

Author's contributions

Conceptualization: LP; Data acquisition: LuP; Genetic analysis, MEO, EP; Validation, VN; Supervision, writing original draft, review & editing: LP.

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