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Case Report

Glycogenin-1 deficiency mimicking limb-girdle muscular dystrophy

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ABSTRACT

Glycogen storage disease type XV (GSD XV) is a recently described muscle glycogenosis due to glycogenin-1 (*GYG1*) deficiency characterized by the presence of polyglucosan bodies on muscle biopsy (Polyglucosan body myopathy-2, PGBM2). Here we describe a 44 year-old man with limb-girdle muscle weakness mimicking a limb-girdle muscular dystrophy (LGMD), and early onset exertional myalgia. Neurologic examination revealed a waddling gait with hyperlordosis, bilateral asymmetric scapular winging, mild asymmetric deltoid and biceps brachii weakness, and pelvic-girdle weakness involving the gluteal muscles and, to a lesser extent, the quadriceps. Serum creatine kinase levels were slightly elevated. Electrophysiological examination showed a myopathic pattern. There was no cardiac or respiratory involvement. Whole-body muscle MRI revealed atrophy and fat replacement of the tongue, biceps brachii, pelvic girdle and erector spinae. A deltoid muscle biopsy showed the presence of PAS-positive inclusions that remained non-digested with alpha-amylase treatment. Electron microscopy studies confirmed the presence of polyglucosan bodies. A diagnostic gene panel designed by the Genetic Diagnosis Laboratory of Strasbourg University Hospital (France) for 210 muscular disorders genes disclosed two heterozygous, pathogenic *GYG1* gene mutations (c.304G > C;p.(Asp102His) + c.164_165del).

Considering the clinical heterogeneity found in the previously described 38 GYG-1 deficient patients, we suggest that *GYG1* should be systematically included in targeted NGS gene panels for LGMDs, distal myopathies, and metabolic myopathies.

1. Introduction

Polyglucosan body myopathy-2 (PGBM-2 OMIM #616199, POLYGLUCOSAN BODY MYOPATHY 2), or glycogen storage disease type XV (GSD XV), is a recently described muscle glycogenosis due to glycogenin-1 deficiency. Glycogenin-1, acting at the first step of glycogen synthesis, is a glycosyl-transferase that catalyzes the formation of a short glucose polymer of approximately 10 glucose residues from uridine diphosphate glucose, in an auto-glucosylation reaction [1]. The histopathological hallmark of this disease is the presence of polyglucosan bodies, characterized by abnormally structured glycogen not digested by alpha amylase. The presence of polyglucosan bodies is also observed in rare muscle glycogenoses such as branching enzyme deficiency (GSDIV), phosphofructokinase deficiency (GSDVII), and *RBCK1*-related polyglucosan body myopathy (PGBM-1, OMIM #615895. POLYGLUCOSAN BODY MYOPATHY 1 WITH OR WITHOUT IMMUNODEFICIENCY).

Autosomal recessive PGBM2 usually starts in adulthood and manifests striking heterogeneity of muscle weakness distribution distinguishing this disorder from other muscle glycogenoses. To date, fewer than 40 cases have been reported in the literature, and several studies highlighted the frequency of asymmetry and distal limb weakness [1–3]. Here we describe a PGBM-2 patient presenting with limb-girdle muscle weakness mimicking limb-girdle muscular dystrophy (LGMD).

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2. Case report

A 44 year-old man, born to non-consanguineous French parents and without any family history of muscle disease, presented for evaluation. He acquired normal motor milestones but, during childhood, he complained of exertional myalgia without limitation during sports activities. Lower limb weakness appeared at 25 years. The course was slowly progressive leading to interruption of sports activities at the age of 28 years. In the following years, he complained of increasing difficulties rising from a chair and climbing stairs.

Physical examination at the age of 44 year revealed a waddling gate with hyperlordosis, and bilateral asymmetrical scapular winging, predominant on the right side (Fig. 1). There were no contractures. Both deltoids and vastus lateralis were atrophic. There was a mild asymmetric weakness of the deltoids and biceps brachii (graded 4/5 with MRC scale on the left, and 5/5 on the right), without limitation of active arm abduction and elevation. Pelvic-girdle weakness was more prominent in the gluteus medius (2/5 on both sides) and maximus (4/5 on the left and 3/5 on the right), with a milder involvement of the quadriceps (4/5 on the left). Mild, symmetric ankle dorsiflexion weakness was also detected (graded 4/5). There was no clinical axial weakness but the abdominal muscles appeared flaccid and hypotonic. Finally, a slight facial asymmetry was observed with right-side ptosis and mild tongue weakness. There were neither sensory nor cognitive symptoms.

Serum creatine kinase levels were slightly elevated to 600 UI/L. Electrophysiological examination found normal motor and sensory conduction studies on median, ulnar, and left tibial and fibular nerves. Needle electromyography revealed myopathic features in brachioradial, tibialis anterior and left gluteus maximus. Electrocardiogram, cardiac ultrasound and pulmonary function tests were normal (Vital capacity 4.87 L sitting [106% of the normal] and 4.51 L in decubitus [96%], PE 101 cmH20 [78%], PI 82 cmH2O [84%], SNIP 79 cmH2O [73%]).

Whole-body muscle MRI (Fig. 2) with coverage of the total body length, using a 3 T magnet system, was performed with axial 5 mm thick, contiguous, multi-stack IDEAL T2 (3 points Dixon Technique) auto-binded slices. Fat images similar to T1-weighted images and water images similar to T2 with fat saturation or STIR images were obtained. A complement of 3D T1 weighted sequences from head to pelvis was made. The MR examination revealed atrophy and fat replacement of the abdominal belt and erector spinae (Fig. 2E to H), the pelvic girdle (Fig. 2I) and biceps brachii in upper limbs (J). Muscle involvement was less evident in the face (except tongue, fatty replaced, Fig. 2C), scapular girdle and lower limbs (Fig. 2N). The involvement was quite symmetric and there was no bright signal on Water images (T2 fat saturated images).

A right deltoid muscle biopsy (Fig. 3) showed the presence of PAS positive inclusions (Fig. 2A) that remained incompletely digested with alpha amylase treatment. Electron microscopy studies confirmed the presence of partly filamentous material corresponding to polyglucosan bodies (Fig. 2B).

A molecular diagnosis was made based on a gene panel designed by

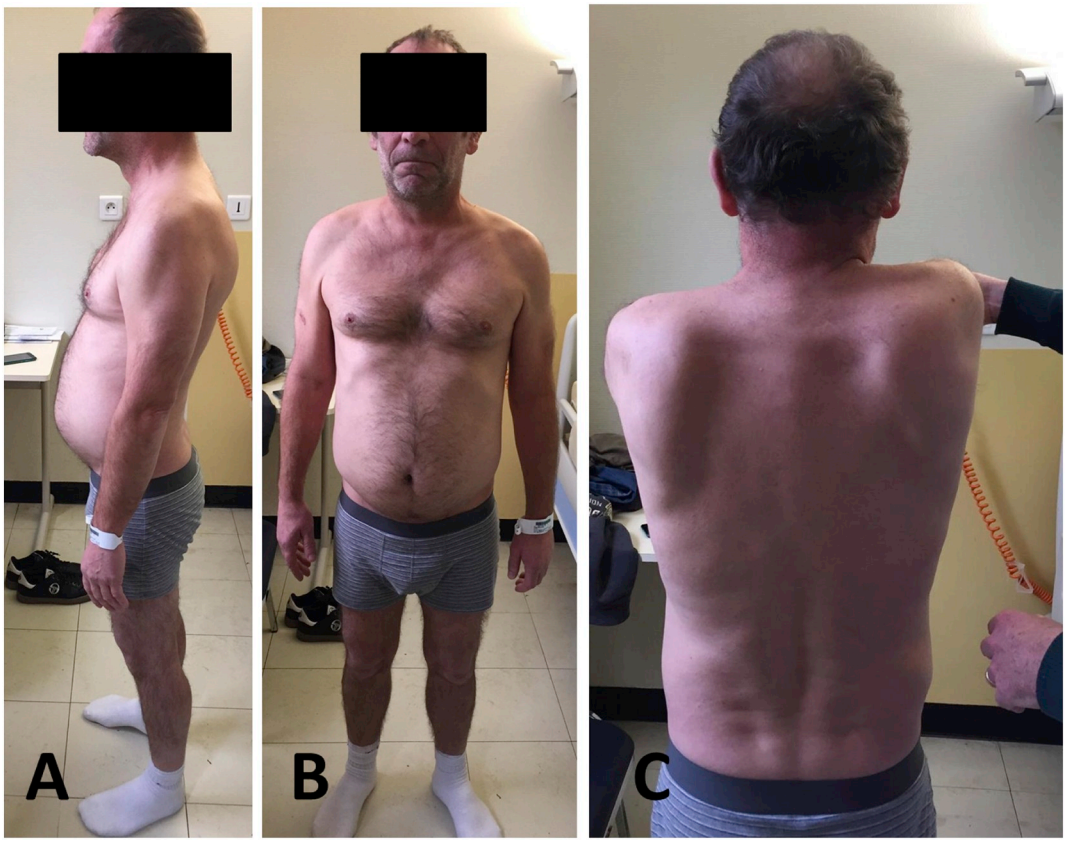

Fig. 1. clinical examination.
A. Lumbar hyperlordosis with prominent abdomen.
B. Bilateral deltoid and *vastus lateralis* amyotrophy.
C. Asymmetric scapular winging (> right). right side.

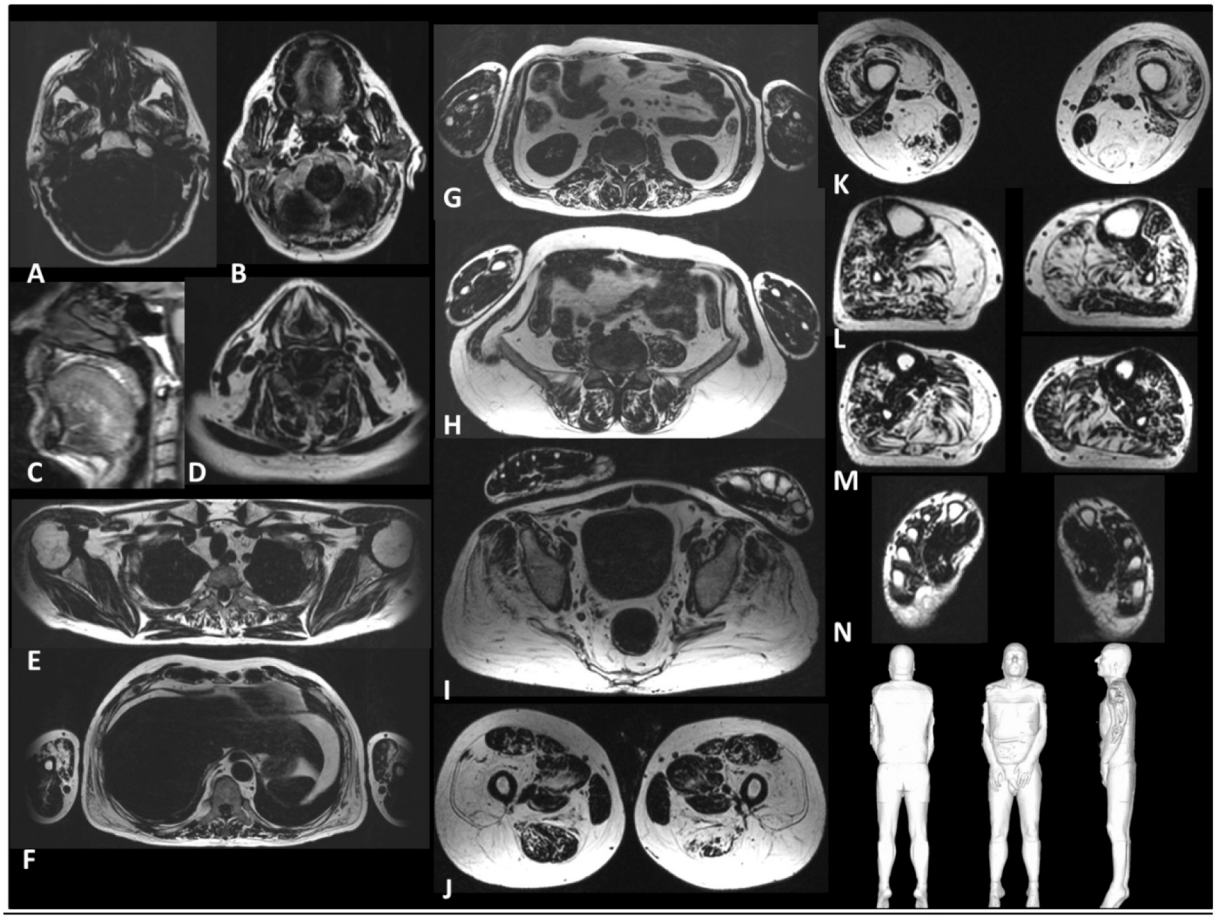

Fig. 2. Muscular RMI: full body RMI examination.
Selection of 12 slices within the 350, 5 mm thick, contiguous axial slices from head to toe, DIXON T2 (IDEAL T2) fat images (A, B and D to N); sagittal reconstruction of the T1 weighted 3D frontal sequence centered on the tongue (C) and 3D volume rendering reconstructions (obtained by the post-processing of the axial IDEAL sequence) with posterior, anterior and lateral views.
These 3D views allow a global analysis of the phenotypes of the patients.
In fat images, the fat tissue provides a bright signal (white) and preserved muscles (not fatty infiltrated muscles) show a very low signal (black), whereas fatty infiltration in muscles is responsible for an increase of signal intensity.
Muscle involvement is less evident in the face (except tongue, fatty replaced, C) and scapular girdle.
In trunk (E to H), the abdominal belt, as well as erector spinae, are atrophied and fat-replaced.
In pelvic girdle (I), the glutei are quite totally fat-replaced.
In upper limbs, (J) the biceps brachialis are atrophied and fat-replaced, forearms are preserved.
In lower limbs: (K to N).

- In thigh, rectus femoris, adductor longus, gracilis and sartorius are better preserved. Semi-membranous, semi-tendinous and biceps of the thigh are more involved.
- In legs, tibialis anterior, lateral gastrocnemius and flexor digitorum are better preserved.
- Feet (N) are preserved.

The involvement is quite symmetric and there is not a bright signal on Water images (T2 fat saturated images).

the Genetic Diagnosis Laboratory of Strasbourg University Hospital (France) which examined 210 genes known to be involved in muscular disorders. Two heterozygous mutations in GYG1 gene were found. One was the previously reported c.304G > C; p.(Asp102His) variant [4] and the other a novel truncating mutation (c.164_165del, p.(Phe55*)). The patient is likely compound heterozygous based on NGS reads. Segregation studies were not performed. However, the patient's parents, his sister and brother are reportedly unaffected.

3. Discussion

Our PGBM-2 patient presented with a LGMD weakness pattern mimicking Pompe disease, and thus confirming the great clinical variability of GYG1-related glycogenoses [2]. Among the previously reported cases of PGBM2, the majority showed proximal limb muscle weakness (19/36; 52.8%), 13% had distal weakness (5/36; 13.6%), and a proximo-distal weakness distribution was found in 22.2% (8/36). Asymmetric clinical distribution, also noticed in our patient, was noticed in 5 patients [1,3,5,6]. Although our patient failed to show cardiac involvement, cardiac abnormalities, not always related to the disease, were found in 40.7% of previously-reported GYG1 (13/32) patients, and three cases had an isolated cardiopathy with the presence of polyglucosan bodies on cardiac muscle biopsy [7]. The skeletal or cardiac muscle selectivity in GYG1 related disorders remains unexplained. Serum CK levels were normal (20/29; 69.0%) or mildly elevated up to 1500 UI/L (Table 1).

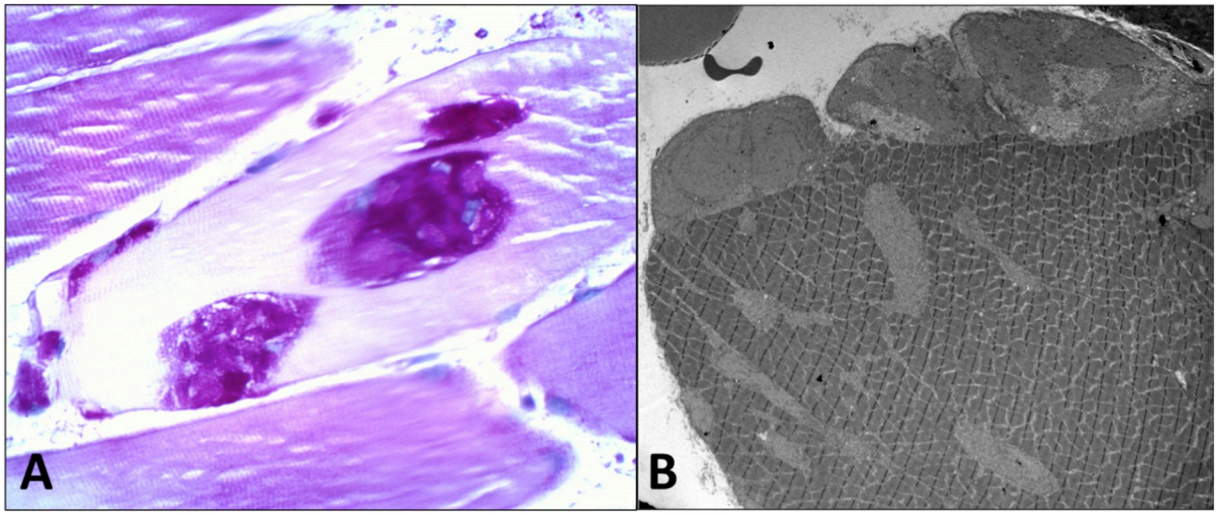

Fig. 3. Muscle morphology: deltoid muscle biopsy.

A. Semithin section, PAS staining, 25×. Presence of round PAS positive inclusions inside the muscle fiber corresponding to polyglucosan bodies. Note the lobulated structure of polyglucosan bodies. The rest of the myofiber shows faint PAS staining.
B. Electron micrograph showing the presence of multiple subsarcolemmal and cytoplasmatic bodies composed by partly filamentous material intermingled with glycogen granules. The sarcomeric structure is overall conserved.

Table 1
Review of the 36 reported cases of glycogen storage disease type XV induced by recessive glycogenin-1 mutation.

		nb/total data	%
Sex repartition	Females	17/35	48.6
Muscular phenotype of symptomatic patient	Proximal	19/36	52.8
	Distal	5/36	13.2
	Proximo-distal	8/36	22.2
Age at the onset (in years)	≤30 y	9/36	25.0
	31–50 y	14/36	38.9
	> 50 y	13/36	41.7
Cardiac disorder[a]		13/32	40.6
Elevation of CK in serum	*N* > 180 UI/L	9/29	31.0
	[min-max]	183–1509	
Electroneuromyography pattern	Myopathic	25/26	96.2
	Neurogenic	4/26	15.4
	Fibrillation	5/26	19.2
	Myotonia	1/26	3.8
Presence of vacuoles PAS+ in muscular biopsy	Presence	27/29	93.1
Molecular statut diagnosis	Homozygote	22/37	59.5

- Histopathological confirmation on myocardial muscle had been performed for only 4 patients: 3 patients with isolated cardiac disorder (2 heart transplantations, 1 very extensive (> 50%) late gadolinium enhancement in a non-ischaemic pattern) and for 1 patient with arrhythmia associated with proximal muscle weakness.
- The others had cardiac abnormalities without histopathological confirmation (number of patients): arrhythmia [1], ischemic cardiopathy [2], valvulopathy [4], conduction disorder [1], pulmonary artery hypertension [1].

Review of 36 cases reported in the literature from 2010 to 2019 [1–7,9,11–15].
- Glycogenin-1 Deficiency and Inactivated Priming of Glycogen Synthesis, Moslemi 2010 (1 case).
- Muscle pathology and whole-body MRI in a polyglucosan myopathy associated with a novel glycogenin-1 mutation, Luo 2015 (1 case).
- GYG1 gene mutations in a family with polyglucosan body myopathy, Fanin 2015 (3 cases).
- A new muscle glycogen storage disease associated with glycogenin-1 deficiency, Malfatti 2014 (7 cases).
- Late-onset polyglucosan body myopathy in five patients with a homozygous mutation in GYG1, Akman 2016 (5 cases).
- Start codon mutation of GYG1 causing late-onset polyglucosan body myopathy with nemaline rods, Tasca 2016 (1 case).
- Cardiomyopathy as presenting sign of glycogenin-1 deficiency-report of three cases and review of the literature, Odfors 2017 (3 cases).
- Glycogen Synthesis in Glycogenin 1-Deficient Patients: A Role for Glycogenin 2 in Muscle, Krag 2017 (2 cases).
- Clinical heterogeneity and phenotype/genotype findings in 5 families with GYG1 deficiency, Ben Yaou 2017 (9 cases).
- Severe asymmetric muscle weakness revealing Glycogenin-1 polyglucosan body myopathy, Stojkovic 2017 (1 case).
- Polyglucosan myopathy and functional characterization of a novel GYG1 mutation, Hegberg- Oldfors 2018 (2 cases).
- GYG1 causing progressive limb girdle myopathy with onset during, Desikan 2018 (1 case).
- Functional characterization of GYG1 variants in two patients with myopathy and glycogenin-1 deficiency, Oldfors 2019 (2 cases).

[a] Cardiac disorder described for 13 patients with glycogenin-1 recessive mutation.

Whole-body muscle MRI was a valuable tool orienting us towards the diagnosis of PGBM2. While the loss of skeletal muscle mass or muscle atrophy was clinically suggestive, it was precisely quantified with MRI. Accumulation of intra- and intermuscular fat in IDEAL T2 sequences was evident with a high signal (white), similar to subcutaneous fat. They were both linked to loss of muscle strength and were a subclinical clue of muscle frailty. We describe herein a specific pattern consisting of fatty replacement of the tongue such as in Late Onset Pompe disease (LOPD) [8], with preservation of sub-scapular muscles, in contrast with LOPD. Moreover, these patients show higher levels of fatty replacement than atrophy. Concordantly, our patient showed prominent atrophy of back muscles more than fatty replacement. Regarding the MRI pattern, the conservation of the tibial anterior in contrast to a hugely fatty replaced medial gastrocnemius [4,9] is a strong argument against facioscapulohumeral dystrophy (FSHD1), despite the presence of slight asymmetric muscle involvement in the thighs. T2 bright signal in muscle associated with an increase of water content or "inflammatory signal" can be observed in FSHD and Pompe disease before the fatty replacement onset but is absent from the whole-body RMI of our patient.

From a histopathologic standpoint, the muscle biopsy was consistent with those of a large majority of PBM-2 patients, showing accumulation of polyglucosans bodies (27/29; 93.1%). The morphologic features of GYG1-related polyglucosan help distinguish PGM2 from other rare polyglucosan body myopathies such as glycogenosis including branching enzyme or phosphofructo-kinase deficiencies, and *RBCK1* mutations in that PGBM2 muscles harbor bigger round or oval subsarcolemmal or cytoplasmic inclusions sometimes including myonuclei, ultrastructurally characterized by a lobulated grape structure is always present and each acinus is separated by a thin rim of normally structured and electron dense glycogen granules [10].

Molecular analysis through a NGS panel revealed compound heterozygous mutations, which did not include the most recurrent one (the c.143 + 3C > G intronic variant). Indeed, 17 different *GYG1* mutations were found in literature, with the c.143 + 3C > G intronic variant being found in 55.6% of patients (20/36), either in a heterozygous (7/20) or homozygous state (13/20). Specific mutations do not always explain clinical phenotype as shown by Hegberg-Oldfors et al. [4] who described the same genotype in two siblings with, respectively, a proximal *versus* a distal presentation. Recenty, Oldfors and al. [11] described the first case of a heterozygous GYG1 deficient patient with a missense mutation already known in homozygous form in patients with an isolated severe cardiomyopathy, although the patient presented with a severe muscular presentation without any cardiac involvement. However, Malfatti et al. [1] described a patient with the most frequently published mutation in association with a mutation different from either of our patient's but which introduced a premature stop codon (patient 3: c.304G > C and c.749G > A *versus* our patient c.304G > C and c.164_165del). Strikingly, the clinical presentation is also pelvic girdle and peroneal weakness but with sparing of the upper limb, contrary to our patient.

4. Conclusion

Our case report underlines the heterogeneity of clinical presentations of GYG1 deficiency, from LGMD to distal myopathies. That suggests that *GYG1* should be systematically included in NGS gene panels targeted to the diagnosis of LGMD as well as distal myopathies, as well as in gene panels of metabolic myopathies.

Author's contribution

Name	Contribution
Claire LEFEUVRE MD	Investigation, conceptualization, writing original draft, writing review & editing.
Stéphane SCHAEFFER MD	Investigation
Robert-Yves CARLIER MD PhD	Investigation, writing original draft, writing review & editing.
Maxime FOURNIER MD	Investigation
Françoise CHAPON MD PhD	Investigation, writing review & editing.
Valérie BIANCALANA PhD	Investigation, writing review & editing.
Guillaume NICOLAS MD-PhD	Investigation
Edoardo MALFATTI MD PhD	Investigation, writing original draft, writing review & editing.
Pascal LAFORET MD PhD	Investigation, supervision, writing original draft, writing review & editing.

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