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Reply to the comment of Alkan Melikoglu 'Joint manifestations can provide diagnostic clues in Morquio syndrome, a case report'

We read the valuable letter of Alkan Melikoglu entitled "Joint manifestations can provide diagnostic clues in Morquio syndrome, a case report" [1]. We would like to take opportunity to remind important facts about mucopolysaccharidoses (MPS) that should be emphasized, as many clinicians are not familiar with these rare diseases. This lack of awareness, along with MPS great heterogeneity, contributes to underdiagnosis of these pathologies [2].

MPS are a group of rare lysosomal storage diseases including a great number of polymorph syndromes, each being related to a particular mutation responsible for a deficiency of glycosaminoglycan (GAG) degrading enzymes, leading to an accumulation of GAGs in tissues [3] (Table 1).

One key fact about MPS is their great clinical heterogeneity [3,4]. While many of them are diagnosed in children or teenagers, and have a severe prognosis because of organ failure [4], some of them have a mild and more slowly progressive presentation which makes them difficult to recognize. Among these attenuated forms, MPS IV A, also known as Morquio syndrome, is probably more likely to be seen by rheumatologists, for it usually presents with osteoarticular symptoms at the forefront, few or no visceral involvement, and a lifespan that nearly reaches that of the general population [5,6]. Consanguinity is present in up to 20% of the cases, and should always be sought [7]. Furthermore, these milder forms can sometimes mimic inflammatory rheumatic disorders, and therefore be misdiagnosed for a long time, even up to adulthood [8].

As recalled by Melikoglu, skeletal signs are often early features of the disease, and in front of nonspecific symptoms such as joint stiffness and contractures clinicians should particularly look for dysmorphic features, oseochondrodysplasia and dysostis multiplex [8]. Moreover, physicians should always keep in mind that MPS can be responsible for organ impairment, and therefore search for multisystemic manifestations (Table 2).

Diagnosis of these disorders can be complex, and so algorithms have been proposed [9]. When the diagnosis is suspected, the patient should be ideally referred to a reference center for laboratory testing (www.orphanet.org). Quantitative and qualitative

Table 1
Mucopolysaccharidosis (MPS) classification (adapted from [8]). There are 11 known enzymes that give rise to 7 distinct MPS (MPS V and VIII are no longer used). The multiplicity of the enzymes involved in GAGs catabolism and their deficiency account for the numerous subtypes of MPS, but also for the great clinical heterogeneity and various phenotypes inside each subtype. Milder forms more at risk to be later diagnosed in adults (highlighted) are more likely to be found in the subtypes of MPS type I (Scheie syndrome), IVA, VI and VII, because in these forms osteoarticular manifestations prevail, with usually no intellectual deficit, and with fewer visceral injuries. Other types concern almost exclusively infantile diseases with a much shorter life span.

Type	Name	Impaired enzyme	GAG storage material	Transmission	Incidence (1/100,000 live births)	Enzyme replacement therapy
MPS I	Hurler, Scheie, or Hurler-Scheie syndromes	α-L-Iduronidase	DS and HS	Autosomal recessive	0.69–1.66	Laronidase Aldurazyme®
MPS II	Hunter syndrome	Iduronate-2-sulfatase	DS and HS	X-linked recessive[a]	0.3–0.71	Idursulfase Elaprase®
MPS IIIA	Sanfilippo A syndrome	Heparan-N-sulfatase	HS	Autosomal recessive	0.29–1.89	In development
MPS IIIB	Sanfilippo B syndrome	α-N-acetylglucosaminidase	HS	Autosomal recessive	0.42–0.72	
MPS IIIC	Sanfilippo C syndrome	AcetylCoA α-glucosamine acetyltransferase	HS	Autosomal recessive	0.07–0.21	
MPS IIID	Sanfilippo D syndrome	N-acetylglucosamine 6-sulfatase	HS	Autosomal recessive	0.1	
MPS IVA	Morquio A syndrome	Galactosamine-6-sulfate sulfatase	KS and CS	Autosomal recessive[b]	0.22–1.3	Elosulfase alpha Vimizim®
MPS IVB	Morquio B syndrome	β-galactosidase	KS	Autosomal recessive	0.02–0.14	
MPS VI	Maroteaux-Lamy syndrome	Arylsulfatase B	DS	Autosomal recessive	0.36–1.3	Galsulfase Nalgazyme®
MPS VII	Sly syndrome	β-glucuronidase	DS, HS and CS	Autosomal recessive	0.05–0.29	In development
MPS IX	Natowicz syndrome	Hyaluronidase I	HA	Autosomal recessive	< 0.01	

GAG: glycosaminoglycan; DS: dermatan suflate; HS: heparan sulfate; KS: keratan sulfate; CS: chondroitin sulfate; HA: hyaluronic acid or hyaluronan.
[a] Most patients are male.
[b] Parents are consanguineous in up to 20% of the cases.

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Table 2
Potential multisystemic symptoms that may be observed in mucopolysaccharidosis (not exhaustive list).

Osteo-articular	Joint stiffness (except in Morquio syndrome[a]: joint hypermobility of the distal joints contrasting with proximal stiffness)	
	Joint limitation	
	Joint contracture	
	Dysmorphic features	Height variation (from dwarfism to near-normal)
	Osteochondrodysplasia	Pectus excavatum, hyperlordosis, scoliosis, kyphosis, odontoid dysplasia
	Dysostosis multiplex	Hip dysplasia, genu valgum, flat feet
		Dysostogenesis, spondyloepyphyseal dysplasia, spondylometaphyseal dysplasia, platyspondylia
	Early osteoarthritis	Stiffness, chondrodysplasic rheumatism[b]
	Other	Entrapment neuropathy (mainly carpal tunnel syndrome), trigger digits, claw hands (phalangeal contracture)
Dysmorphia	Coarse facies (large nostrils, thick lips and ears, macroglossia, thick hair) Organomegaly	
Neurological	Psychomotor retardation, behaviour trouble, central impairment, peripheral compression, hydrocephalus, compression of the cervical spinal cord (hypoplasia of the dens and atlantoaxial instability)	
Cardiological	Valve disease, myocardial infiltration, coronary heart disease	
Respiratory	Tracheal and bronchial collapse, restrictive pulmonary disease[c]	
Ear, nose and throat/stomatological	Macroglossia, tonsils' hypertrophia, perception deafness, otitis media, recurrent upper tract infections, sleep apnea, dental colorations and gum recession	
Ophtalmological	Lens opacity, corneal clouding, retinopathy, blindness	
Digestive	Inguinal and/or umbilical hernias, hepatomegaly	
Dermatological	Thickened and rough skin texture[d], pebbly papules[e]	

Adapted from [8].

[a] Also known as MPS type IV.

[b] Acute "osteoarthrititic-like" exacerbations in patients with epyphyseal dysplasia, with swollen joints and synovitis, but with mechanic synovial fluid and without any elevation of acute phase reactants.

[c] Due to spinal deformations.

[d] Overall skin texture in patients with MPS can be thickened and rough.

[e] MPS II, and rarely MPS I can be associated with a distinctive skin lesion consisting of white "pebbly" papules 2–10 mm in diameter, sometimes coalescing in ridges.

urine GAG analyses are interesting orientation screening tests, but the biological confirmation requires demonstration of an abnormal plasmatic enzyme activity [3].

Early diagnosis is essential since enzyme replacement therapy is currently available for some subtypes [8] (Table 1), and might, if given early, slow down the development of tissue damage, which is unfortunately irreversible. Beside this specific treatments, the management of MPS should be multidisciplinary, led by an experienced physician in a reference center, and involves at various levels orthopedic surgery and rehabilitative approaches.

In conclusion, as highlighted by Melikoglu, there is a real need to increase awareness of the existence of MPS, especially of attenuated forms, among rheumatologists and other physicians dealing with the musculoskeletal issues, and to improve diagnostic methods. A systematic screening for MPS in rheumatologic or orthopedic patients with joint complaints of unknown etiology would identify 1 case out of 55 [10].

Disclosure of interest

The authors declare that they have no competing interest.

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