Molecular Genetics and Metabolism 114 (2015) 11–18

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Diagnostic evaluation, monitoring, and perioperative management of spinal cord compression in patients with Morquio syndrome

Joel Charrow [a,*], Tord D. Alden [b], Catherine Ann R. Breathnach [c], Geoffrey P. Frawley [d], Christian J. Hendriksz [e], Bianca Link [f], William G. Mackenzie [g,h], Renzo Manara [i], Amaka C. Offiah [j], Martha L. Solano [k], Mary Theroux [l]

[a] Division of Genetics, Birth Defects and Metabolism, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
[b] Division of Neurosurgery, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA
[c] Whitethorn Medical Communications, 130 Old Cassidy Avenue, Lexington, KY 40502, USA
[d] Department of Paediatric Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Australia
[e] Department of Adult Inherited Metabolic Disorders, University of Manchester, Salford Royal NHS Foundation Trust, Clinical Science Building B105, Stott lane, Salford M6 8HD, England, UK
[f] Division of Metabolism, Connective Tissue Unit, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland
[g] Department of Orthopedic Surgery, Nemours/Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803-3607, USA
[h] Jefferson Medical College, 1600 Rockland Road, Wilmington, DE 19803-3607, USA
[i] Neuroradiology, University of Salerno, Via S. Allende 1, 84081, Salerno, Italy
[j] Academic Unit of Child Health, Room C4, Stephenson Wing, Sheffield Children's NHS Foundation Trust, Western Bank, Sheffield, England, UK
[k] Department of Neuropediatrics, Fundación Cardioinfantil, Universidad del Rosario, 163rd Street A No. 13B-60, Bogotá, Colombia
[l] Department of Anesthesiology & Critical Care, Nemours/Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803-3607, USA

ARTICLE INFO

Article history:
Received 21 October 2014
Accepted 22 October 2014
Available online 30 October 2014

Keywords:
Atlanto axial fusion
GALNS protein, human
Intubation, endotracheal
MPS IVA
Practice guideline
Spinal cord compression

ABSTRACT

Mucopolysaccharidosis IVA is an autosomal recessive condition caused by mutations in the *GALNS* gene, which encodes N-acetylgalactosamine-6-sulfatase, also called galactosamine-6-sulfatase (GALNS). A reduction in or absence of effective GALNS leads to faulty catabolism of keratan sulfate and chondroitin-6-sulfate within the lysosome; their accumulation causes cell, tissue, and organ dysfunction. The connective tissue, cartilage, ligaments, and bone of patients with Morquio A syndrome are particularly affected. Patients with Morquio A syndrome are at high risk of neurological complications because of their skeletal abnormalities; many patients are in danger of cervical myelopathy due to odontoid hypoplasia and ligamentous laxity leading to atlantoaxial subluxation. The multisystemic involvement of patients with Morquio A syndrome requires treatment by multidisciplinary teams; not all members of these teams may be aware of the potential for subluxation and quadriparesis. A multinational, multidisciplinary panel of 10 skeletal dysplasia or Morquio A syndrome specialists convened in Miami, FL on December 7 and 8, 2012 to develop consensus recommendations for early identification and effective management of spinal cord compression, for anesthesia and surgical best practices, and for effectual cardiac and respiratory management in patients with Morquio A syndrome. The target audience for these recommendations includes any physician who may encounter a patient with Morquio A syndrome, however doctors who do not have access to the full spectrum of specialists and resources needed to support patients with Morquio A syndrome should attempt to refer patients to a center that does. Physicians who manage Morquio A syndrome or comorbid conditions within specialty centers should review these expert panel recommendations and fully understand the implications of spinal cord instability for their own practices.

Contents

Abbreviations: C6S, chondroitin-6-sulfate; ERT, enzyme replacement therapy; GAGs, glycosaminoglycans; *GALNS*, the gene encoding N-acetylgalactosamine-6-sulfatase; GALNS, the protein N-acetylgalactosamine-6-sulfatase, also known as galactosamine-6-sulfate sulfatase; KS, keratan sulfate; MEP, motor evoked potentials; SSEP, somatosensory evoked potentials.

* Corresponding author. Tel.: +1 312 227 6120; fax: +1 312 227 9413.
E-mail addresses: jcharrow@northwestern.edu (J. Charrow), talden@luriechildrens.org (T.D. Alden), catherine@whitethornmedical.com (C.A.R. Breathnach), geoff.frawley@rch.org.au (G.P. Frawley), Chris.Hendriksz@srft.nhs.uk (C.J. Hendriksz), bianca.link@kispi.uzh.ch (B. Link), wmackenz@nemours.org (W.G. Mackenzie), rmanara@unisa.it (R. Manara), amaka.offiah@nhs.net (A.C. Offiah), docsolano@gmail.com (M.L. Solano), Mary.Theroux@nemours.org (M. Theroux).

http://dx.doi.org/10.1016/j.ymgme.2014.10.010

1. Introduction

Mucopolysaccharidosis IVA (OMIM #253000; eponyms Morquio A, Morquio–Brailsford) is an autosomal recessive condition caused by mutations in the gene encoding N-acetylgalactosamine-6-sulfatase, also known as galactosamine-6-sulfate sulfatase (OMIM #612222) (EC 3.1.6.4) [1–3]. GALNS catabolizes the GAGs KS and C6S [4,5]. A reduction or absence of GALNS activity leads accumulation of KS and C6S and within the lysosome, resulting in cell, tissue, and organ dysfunction. The connective tissue, cartilage, ligaments, and bone of patients with Morquio A syndrome are particularly affected [6,7].

Patients with Morquio A syndrome may appear normal at birth, but bony deformities of the knee, spine, or chest, can appear during the first year of life, although diagnosis may not be made until later [8,9]. The brain and spinal cord are not directly affected by GAG accumulation, and intelligence is preserved, although opportunities for education may be curtailed by physical limitations [10–12]. Many patients are at risk for developing cervical myelopathy due to atlantoaxial subluxation from odontoid hypoplasia and ligamentous laxity. Cervical myelopathy is common in the more severe forms of the disease [13,14].

Although the hallmarks of Morquio A syndrome are skeletal, multiple other systems may be compromised: visual, auditory, digestive, cardiovascular, neurological and respiratory [15]. A variety of surgical procedures may be undertaken in patients with Morquio A syndrome, including decompression/cervical fusion or other spine surgery, myringotomy, hip surgery, osteotomies (especially at the knee), tonsillectomy, adenoidectomy, and herniorrhaphy, and most patients will require multiple procedures [16] by the age of 12 years [8]. A survey of 325 patients with Morquio A syndrome found that more than 70% of patients older than 5 years required some type of surgery [16]. A wide array of specialists care for patients with Morquio A syndrome: anesthesiologists/anaesthetists, cardiologists, geneticists, neurosurgeons, oral surgeons, orthopedic surgeons, otolaryngologists, physical therapists/physiologists, pulmonologists, radiologists, etc.

In addition to monitoring changes in their patients' disease, the Morquio A syndrome-treating physician will have the opportunity to directly or indirectly coordinate care among the full team of specialists on whom their patients rely. Cervical myelopathy arising from atlantoaxial instability is of extreme concern in this patient population, and many non-specialist physicians who treat patients for either skeletal or non-skeletal Morquio A syndrome-related conditions may be unaware of the danger to the spinal cord posed by head and neck manipulations and the risk to the patient of subluxation and quadriparesis [12]. Cardiac and respiratory manifestations of Morquio A have an important impact on surgical risk in these patients.

Therefore, a panel of 10 multinational, multidisciplinary skeletal dysplasia or Morquio A syndrome specialists convened in Miami, FL on December 7 and 8, 2012. Specialties represented on the panel included genetics, metabolic pediatrics, neurosurgery, pediatric anesthesiology, neuroradiology, musculoskeletal radiology, and orthopedic surgery. The panel's goal was to develop consensus recommendations for early identification and effective management of spinal cord compression, for anesthesia and surgical best practices, and for effectual cardiac and respiratory management in patients with Morquio A syndrome.

The target audience for these recommendations includes any physician who may encounter a Morquio A syndrome patient, however doctors who do not have access to the full spectrum of specialists and resources needed to support patients with Morquio A syndrome should attempt to refer patients to a center that does. Physicians who manage Morquio A syndrome or comorbid conditions within specialty centers should review these expert panel recommendations and fully understand the implications of spinal cord instability for their own practices.

This expert panel strongly recommends that every Morquio A syndrome patient undergo all medical assessments, monitoring, and treatments at specialty centers with experience in lysosomal storage disorder management and with a broad network of specialists who can be incorporated into individualized treatment teams. Ideally, these specialty centers would start as the medical home for pediatric patients and continue to provide comprehensive care throughout adulthood.

2. Definitions

Consensus recommendations have been developed based upon expert clinical experience and available scientific evidence.

Expert panel-defined characterizations of spinal instability and cord compression:

1. Spinal instability may occur with or without evidence of spinal cord compression.
2. Spinal cord compression should be expected for most or all patients with Morquio A syndrome but at a wide spectrum of ages, possibly because of distinct Morquio A syndrome phenotypes which have yet to be described genotypically or fully characterized clinically.
3. Although spinal cord decompression for patients with Morquio A syndrome is often necessary at the craniocervical junction, decompression may also be required at multiple spinal cord locations.
4. Cord function, current instability, and the likelihood of future instability are multifactorial considerations when contemplating any surgical intervention. Assessment of cord function by both clinical exam and diagnostic imaging is essential.

3. Recommendations

Patients with Morquio A syndrome have multiple risk factors for myelopathy and paresis: spinal cord compression results from bony stenosis and thickening of soft tissue coupled with ligamentous laxity, deformity, odontoid hypoplasia and atlantoaxial instability. Surgical indications for decompression with or without fusion can be difficult to ascertain [17]. Historically, many physicians performed prophylactic decompression and fusion on young, asymptomatic patients with Morquio A syndrome to prevent cord compression [18,19]. Current