Le mucopolisaccaridosi: il punto di vista del neurologo

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Iscriversi e studiare a Siena

MPS type	Deficient enzyme	Main GAG stored	Neurological symptoms	Somatic symptoms
MPS I	**α-L-iduronidase (EC 3.2.1.76)**	**HS, DS**	**Hurler: severe** **Hurler-Scheie and Scheie: mild to absent**	**Wide spectrum of severity**
MPS II	**Iduronate-2-sulfatase (EC 3.1.6.13)**	**HS, DS**	**Severe (rapidly progressing phenotypes) or mild to absent (slowly progressing phenotypes)**	**Wide spectrum of severity**
MPS IIIA	***N*-sulfoglucosamine sulfohydrolase (EC 3.10.1.1)**	**HS**	**Severe**	**Mild to absent**
MPS IIIB	**α-*N*-acetylgluscoaminidase (EC 3.2.1.50)**	**HS**	**Severe**	**Mild to absent**
MPS IIIC	**AcetylCoA-α-glucosaminide *N*-acetyltransferase (EC 2.3.1.78)**	**HS**	**Severe**	**Mild to absent**
MPS IIID	***N*-acetylglucosamine 6-sulfatase (EC 3.1.6.14)**	**HS**	**Severe**	**Mild to absent**
MPS IVA	*N*-acetylgalactosamine-6- sulfatase (EC 3.1.6.4)	KS	None	Severe or mild
MPS IVB	β-galactosidase (EC 3.2.1.23)	KS	None	Severe or mild
MPS VI	*N*-acetylgalactosamine-4-sulfatase (EC 3.1.6.12)	DS	None	Severe or mild
MPS VII	**β-D-glucuronidase (EC 3.2.1.31)**	**HS, DS**	**Severe (rapidly progressing phenotypes) or mild to absent (slowly progressing phenotypes)**	**Wide spectrum of severity**
MPS IX[a]	Hyaluronidase (EC 3.2.1.35)	Hyaluronan	None	Periarticular soft tissue masses, short stature

DS: dermatan sulfate; GAG: glycosaminoglycan; HS: heparan sulfate; KS: keratan sulfate; MPS: mucopolysaccharidosis.
[a]Few cases described in literature
This review summarizes current knowledge on anatomical and pathophysiological changes associated w

Main Clinical Manifestations of MPS

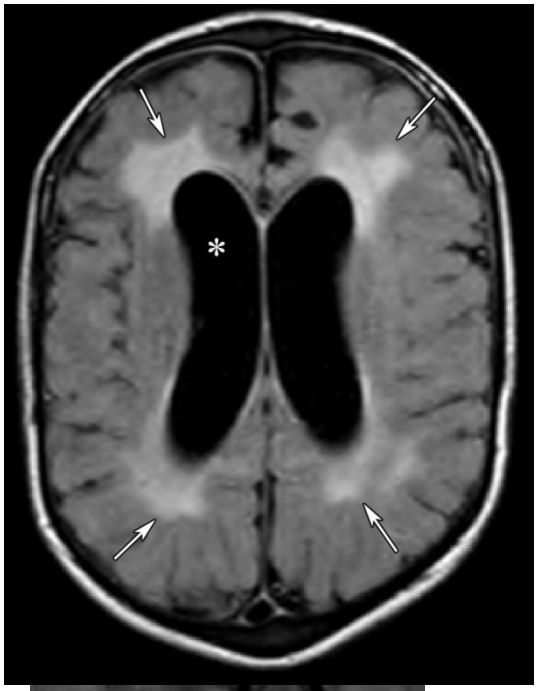
Organ or System	Clinical Manifestations
CNS	Cognitive impairment, behavioral problems, compressive myelopathy
Skeletal system	Dysostosis multiplex, coarse facial features
Eyes	Corneal opacities, retinopathy, glaucoma
Other systems	Hepatosplenomegaly, heart disease, reduced lung function, hearing loss

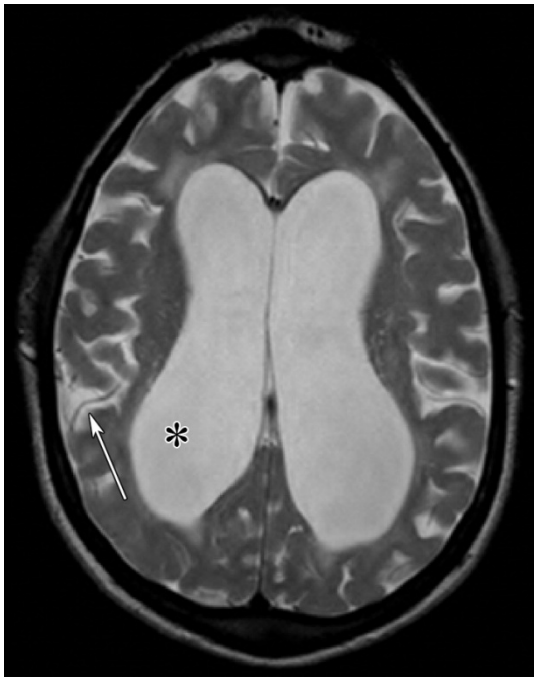
Neuroimaging Findings in MPS and MR Imaging Appearance

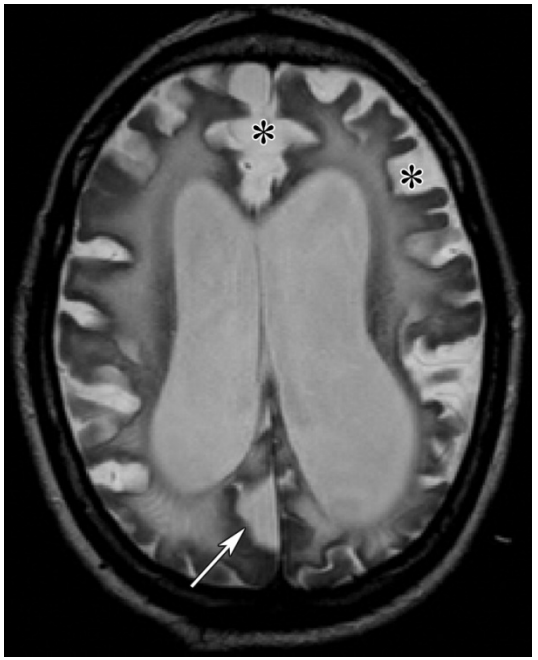
Neuroimaging Finding	MR Imaging Appearance
Enlarged perivascular space	Cribriform or fusiform cystic lesions isointense to cerebrospinal fluid (CSF) at all sequences; diameters ranging from 2 mm to more than 8 mm
White matter lesions	Focal or confluent areas of T1 hypointensity and T2-FLAIR hyperintensity
Hydrocephalus	Dilatation of ventricular spaces typically associated with enlarged subarachnoid spaces
Cortical atrophy	Enlargement of cortical sulci and fissures
Cervical spinal canal stenosis	Dysplastic odontoid process associated with soft-tissue mass, which is usually iso- or hypointense on T1-weighted images and hypointense on T2-weighted images, with or without spinal cord compression and myelopathy; functional imaging of the cervical spine may be necessary to better depict atlantoaxial instability
Bone abnormalities in the skull and spine	Wedge-shaped vertebral bodies, platyspondyly, anterior beaking with posterior scalloping of vertebral bodies (bullet-shaped vertebrae), intervertebral disk changes, gibbus deformity, scoliosis, odontoid dysplasia, thickening of the diploe, morphologic abnormalities of the sella turcica, and macrocephaly

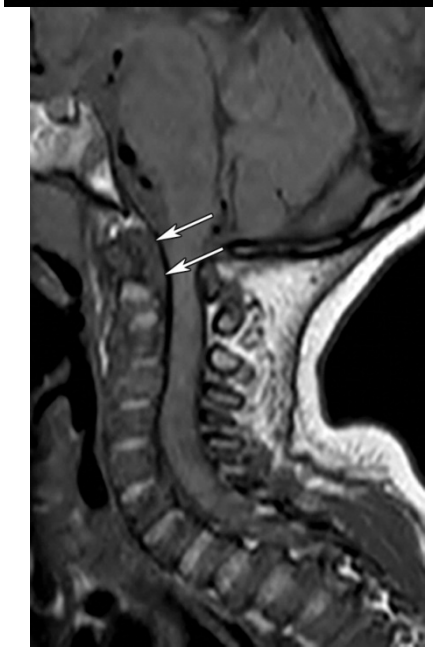
Neuroimaging Findings in MPS and MR Imaging Appearance

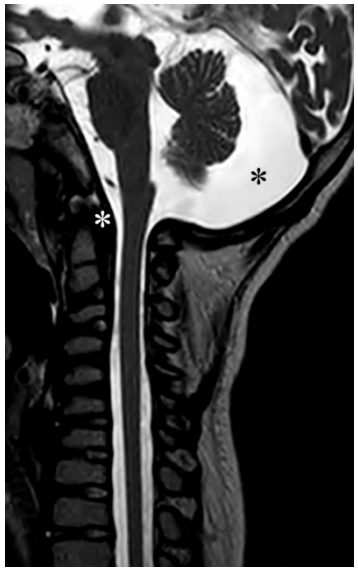
Type of MPS	Enlarged Perivascular Space	White Matter Lesions	Hydrocephalus	Brain Atrophy	Spinal Canal Stenosis	Dysostosis Multiplex
MPS I	Typical and pronounced	Typical and pronounced	Typical and pronounced	Typical and pronounced	Typical	Typical and pronounced
MPS II	Typical and pronounced	Typical and pronounced	Typical and pronounced	Typical and pronounced	Typical	Typical and pronounced
MPS III	Typical	Typical and pronounced	Typical	Typical and pronounced	Typical	Uncharacteristic
MPS IV	Uncharacteristic	Typical	Typical	Uncharacteristic	Typical and pronounced	Typical and pronounced
MPS VI	Typical	Typical	Typical	Typical	Typical and pronounced	Typical and pronounced
MPS VII	Uncharacteristic	Typical and pronounced	Uncharacteristic	Uncharacteristic	Typical	Typical and pronounced
MPS IX	Uncharacteristic	Uncharacteristic	Uncharacteristic	Uncharacteristic	Uncharacteristic	Uncharacteristic









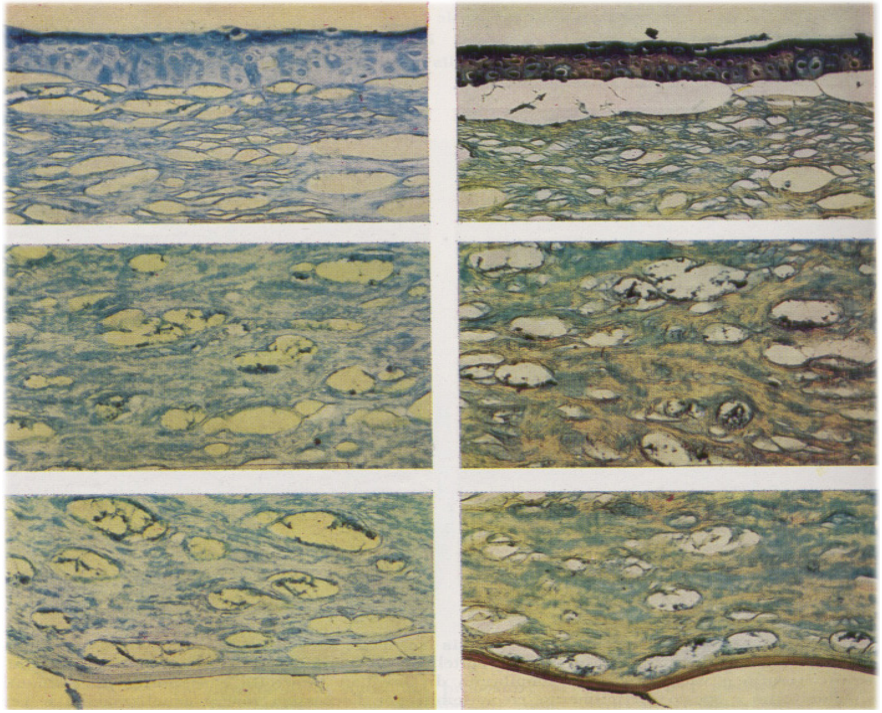


Radiographics. 2016 Sep Oct; 36(5): 1448-62. doi: 10.1148/rg.2016150168.

Neuroimaging Findings in Patients with Mucopolysaccharidosis: What You Really Need to Know.

Reichert R[1], Campos LG[1], Vairo F[1], de Souza CF[1], Pérez JA[1], Duarte JÁ[1], Leiria FA[1], Anés M[1], Vedolin LM[1].

La prima famiglia italiana di
Malattia di Scheie,
Acta Neurol 26: 143, 1971



Esame istochimico della cornea
in un nuovo paziente.
Acta Neurol 29: 38, 1974

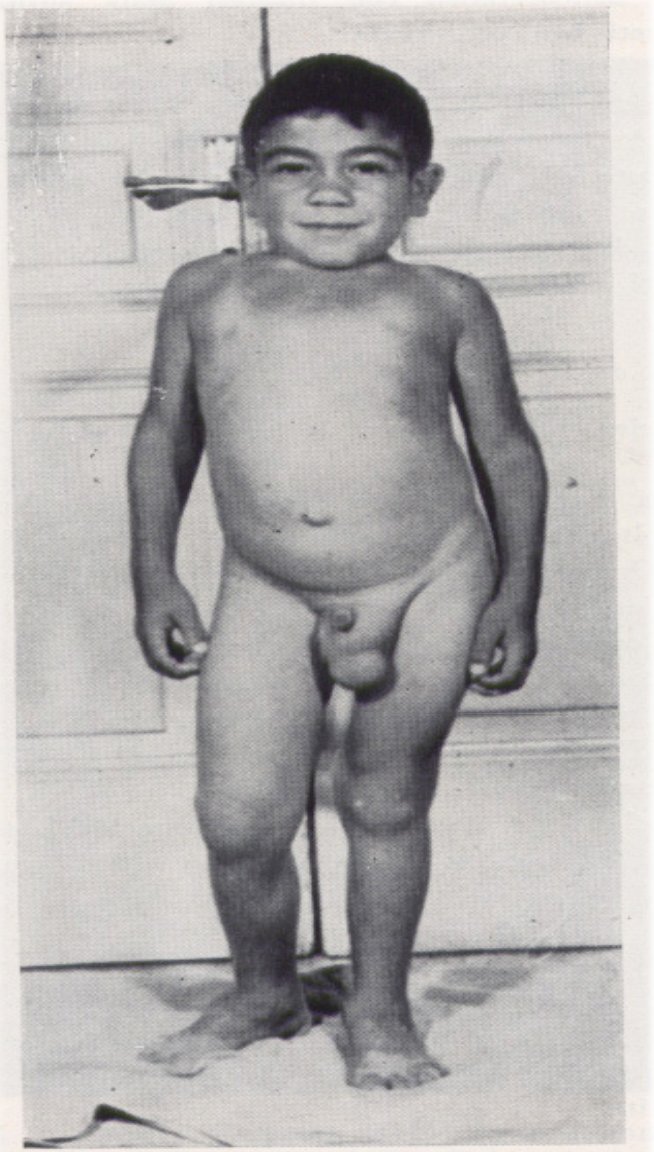
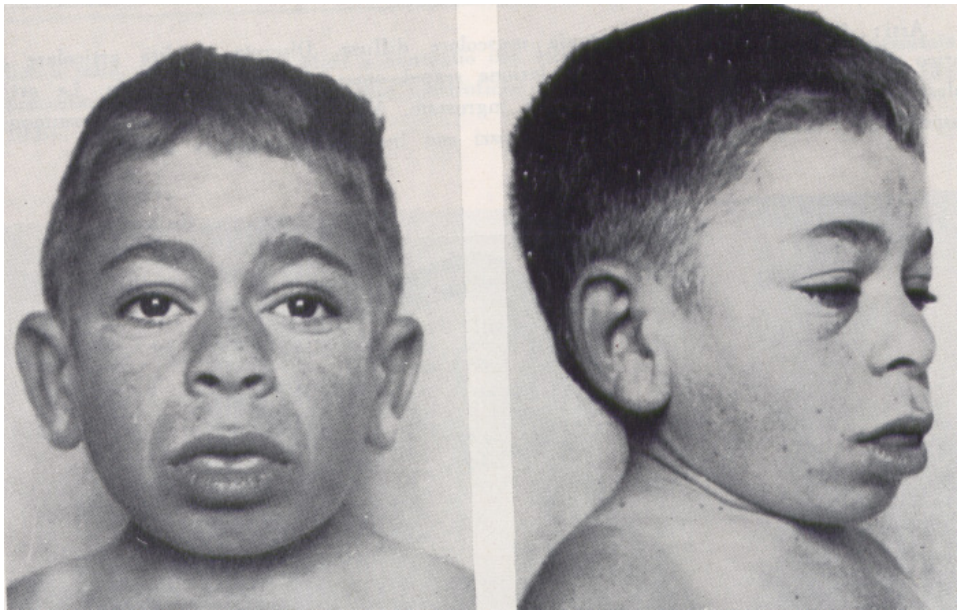
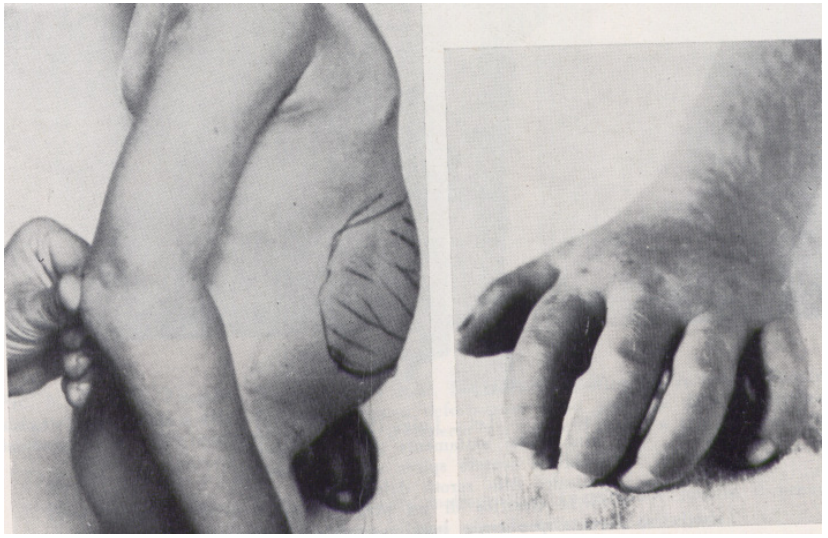
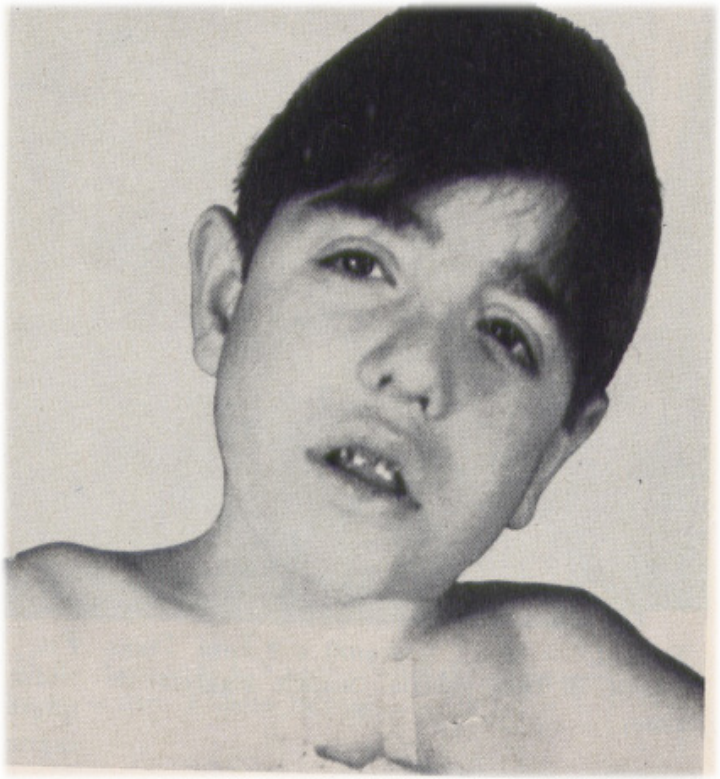


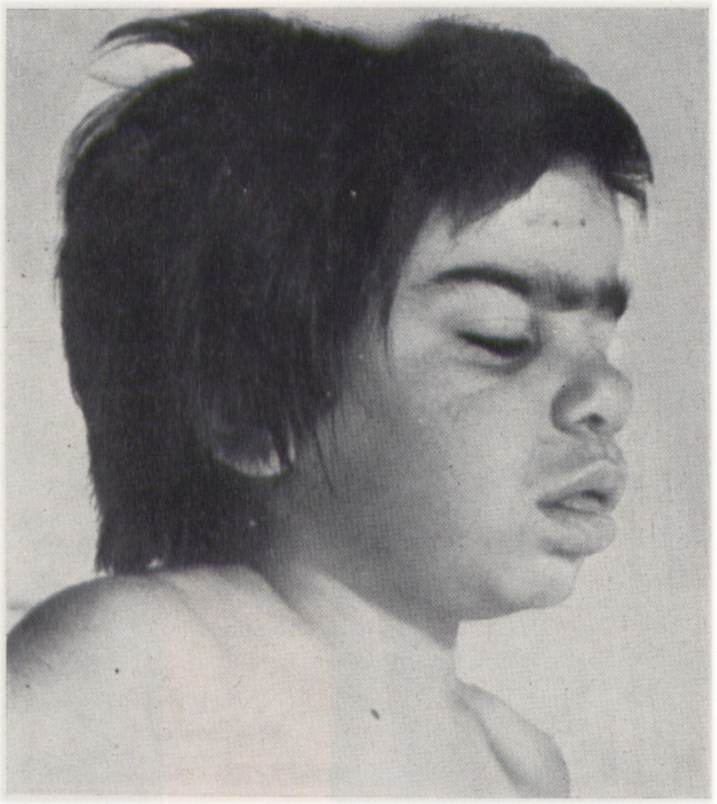
FIG. 6. — Abb... Leopoldo (III, 21) a 10 anni. Facies ormai chiaramente gargoilica. A sinistra è comparsa una voluminosa ernia inguino-scrotale.





Malattia di Hunter Acta Neurol 18: 323, 1973





Malattia di Sanfilippo

Acta Neurol 29: 231, 1974

FEBS Lett. 2018 Mar 7. doi: 10.1002/1873-3468.13026. [Epub ahead of print]

Proteoglycans in brain development and pathogenesis.

Schwartz NB[1,2], Domowicz MS[1].

Abstract

Proteoglycans are diverse, complex extracellular/cell surface macromolecules composed of a central core protein with covalently linked glycosaminoglycan (GAG) chains; both of these components contribute to the growing list of important bio-active functions attributed to proteoglycans. Increasingly, attention has been paid to the roles of proteoglycans in nervous tissue development due to their highly regulated spatio/temporal expression patterns, **whereby they promote/inhibit neurite outgrowth, participate in specification and maturation of various precursor cell types, and regulate cell behaviors like migration, axonal pathfinding, synaptogenesis and plasticity.** These functions emanate from both the environments proteoglycans create around cells by retaining ions and water or serving as scaffolds for cell shaping or motility, and from dynamic interactions that modulate signaling fields for cytokines, growth factors and morphogens, which may bind to either the protein or GAG portions. Also, genetic abnormalities impacting proteoglycan synthesis during critical steps of brain development and response to environmental insults and injuries, as well as changes in microenvironment interactions leading to tumors in the central nervous system, all suggest roles for proteoglycans in behavioral and intellectual disorders and malignancies.

Proteoglycan functions in the CNS

GAG-proteoglycan interactions are critical to basic processes of CNS establishment and maintenance, including cellular proliferation, migration, specification, synaptogenesis, plasticity and regeneration.

Migration

Following neurogenesis and establishment of neuronal identity, postmitotic neurons migrate to their final functional positions *via* different mechanisms. Some, especially newborn neurons from the ventricular zone (VZ), move along radial glial fibers to form the layers of the cerebral cortex. These new neurons initially exhibit multi-polar morphology and migrate in random directions in the subventricular and intermediate zones until they reach the subplate, where they transform into a bipolar shape, attach to the radial glial fibers, and rapidly migrate toward the cortex. This migration mode involves HSPGs, that is, syndecans (SDE3) play an essential role, as mice lacking SDE3 have a disorganized cortical laminar structure due to impaired radial migration along the glial fibers . This phenotype may be mediated *via* pleiotrophin, which binds to the HS of SDE3 and is required for pleiotrophin-induced neural migration.

As mentioned, growth/migration-promoting factors like pleiotrophin and midkine also bind to CSPGs *via* both the latter's core protein and GAG portions . In particular, neuronal cell-surface PTPRZ1 and secreted phosphacan bind pleiotrophin with high affinity , which induces migration of cortical neurons , and this pleiotrophin-induced neuronal migration can be competitively inhibited by phosphacan and free CS GAGs . These findings indicate that soluble CSPGs like phosphacan and NCAN may also regulate the migratory behavior of neurons by inhibiting the pleiotrophin-PTPRZ1 signaling.

Cell specification

During development, the brain is formed from the simple neuroepithelium that lines the cerebral ventricles and spinal column in a complex but orderly sequence of events. Differentiation occurs from radial glia precursors in a progressive sequence of neurogenesis, followed by gliogenesis, which then depletes radial glia precursors from the VZ leaving only two adult neurogenesis niches . Complex changes in the PGs found in stem cell niches occur during brain development . For example, expression of various members of the HSPG-glypican family are developmentally regulated in the VZ during neurogenesis: GPC4 is expressed in neural stem cell, GPC1 is expressed in postmitotic neurons , GPC2 and GPC5 are only expressed in committed neurons ; knockout of GPC1 results in a reduction in brain size, impairment in FGF signaling and premature differentiation of postmitotic neurons . Other HSPGs, for example, perlecan, occur in the basal lamina, and null mutants exhibit a reduction in early precursors, impaired cell-cycle progression and microcephaly ; while SDE1 and SDE4 localize to the VZ along with neural precursors, and knockdown of these PGs decreases neural stem cell proliferation and induces premature neuronal differentiation .

Reduction in function of CSPGs *via* chondroitinase injection into the ventricles during neurogenesis suggests a role for CSPGs in precursor self-renewal, proliferation and differentiation during the neuron-glial differentiation switch . Other CSPGs are associated with the gliogenesis process; for example, ACAN and BCAN in axons start to be expressed in radial glia of the VZ during the switch from neuronal to glial precursor production ; knockout of ACAN increases precursor differentiation to the astrocytic lineage in the avian brain .

Proteoglycan functions in the CNS

Axonal guidance and pathfinding

The participation of GAGs in axon guidance and pathfinding in both the peripheral and CNS is well established. As neurons extend axonal processes toward synaptic partners, numerous attractive and repulsive guidance cues facilitate this navigation process. Most of the major guidance cues such as netrins (attractant), slits (repellant) and ephrins bind HSPGs with high affinity . Expression of HS by neurons enabling their axons to respond to cues, was demonstrated in Nestin-cre; EXT1 conditional knockout mice which lack HS in the nervous system and have major axon-guidance defects, including absence of commissural tracts and retinal axon errors . Mouse mutants lacking the HS-modifying enzyme NDST1 exhibit axon-guidance defects similar to EXT1 knockout, including absent or hypoplastic anterior and hippocampal commissures 55. These results suggest that HS chains as well as their specific sulfation motifs are important to axonal-guidance function.

CSPGs also participate in axonal pathfinding in different areas of the brain and at different developmental stages. Although no biosynthetic knockout model of any CSPG nor of the common chondroitin-6- sulfotransferase , has exhibited defects in axonal pathfinding, experiments that reduce CS content with chondroitinase treatment have shown that CSPGs are involved in fasciculation of axons mediated by SEMA5A 1, modulation of retinal axon growth toward the optic nerve and across the chiasm , and prevention of axons from crossing the midline when they reach the optic tectum .

Synaptogenesis and plasticity

The formation of functional synaptic connections is essential for neuron-target interactions. Synapses enable the transmission of information between neurons or between neurons and muscle in the neuromuscular junction. Presynaptic axonal termini release neurotransmitters into the synaptic cleft which then bind receptors on the postsynaptic membrane of target neuronal dendrites or muscle fibers. Several HSPGs are required for synaptic function; SDC2 is important to the synapse formation process , *via* interaction with a variety of synaptic adaptor proteins like CASK, synbindin and synectin required for spine formation , neurofibromin which promotes filopodia formation , and the EphB2 receptor tyrosine kinase required for SDC2 clustering on dendrites and induction of dendritic spines . Glypicans (GPC4) are the presynaptic partners of the postsynaptic transmembrane protein LRRTM4 ; this interaction fosters binding of GPC4 with PTPRS (protein tyrosine phosphatase receptor type S) , required for excitatory synapse development in a HS dependent manner. Astrocytes also secrete GPC4 and GPC6, which promote excitatory synapse formation in retinal ganglion cells *via* clustering of glutamate receptors

CSPGs also are important in synapse stabilization and maturation, mainly as components of perineuronal nets (PNNs), the specialized matrices that surround neurons and their dendrites in the CNS. ACAN expression is upregulated postnatally during PNN formation, while NCAN, VCAN and phosphacan/PTPRZ1 are all components of PNNs . Functional consequences of CS chain degradation with chondroitinase and disassembly of PNNs include: ocular dominance ; fear memory resilience ; and enhancement of long-term recognition memory . Interestingly, the axon-guidance protein, SEMA3, which interacts with CSPGs and HSPGs and the CSPG receptors LAR (leucocyte common antigen-related phosphatase) and NOGO have also been localized to PNNs. Clearly, expression and localization of CNS PGs contribute to many fundamental development processes including axon guidance and regulation of synaptic plasticity.

Glycosidases and cerebellar ontogenesis in the rat. Zanetta JP, **Federico A**, Vincendon G.

J Neurochem. 1980 Apr;34(4):831-4.

Glycoprotein changes during the development of human brain. **Federico A**, Di Benedetta C.

J Neurochem. 1978 Oct;31(4):797-800

Neurochem Res. 2011 Jul;36(7):1228-40. doi: 10.1007/s11064-010-0324-y. Epub 2010 Nov 26.

Functions of chondroitin sulfate and heparan sulfate in the developing brain.

Maeda N[1], Ishii M, Nishimura K, Kamimura K.

Abstract

Chondroitin sulfate and heparan sulfate proteoglycans are major components of the cell surface and extracellular matrix in the brain. Both chondroitin sulfate and heparan sulfate are unbranched highly sulfated polysaccharides composed of repeating disaccharide units of glucuronic acid and N-acetylgalactosamine, and glucuronic acid and N-acetylglucosamine, respectively. During their biosynthesis in the Golgi apparatus, these glycosaminoglycans are highly modified by sulfation and C5 epimerization of glucuronic acid, leading to diverse heterogeneity in structure. Their structures are strictly regulated in a cell type-specific manner during development partly by the expression control of various glycosaminoglycan-modifying enzymes. **It has been considered that specific combinations of glycosaminoglycan-modifying enzymes generate specific functional microdomains in the glycosaminoglycan chains, which bind selectively with various growth factors, morphogens, axon guidance molecules and extracellular matrix proteins. Recent studies have begun to reveal that the molecular interactions mediated by such glycosaminoglycan microdomains play critical roles in the various signaling pathways essential for the development of the brain.**

Metab Brain Dis. 2015 Dec;30(6):1343-8. doi: 10.1007/s11011-015-9684-y. Epub 2015 May 29.

Mental retardation in mucopolysaccharidoses correlates with high molecular weight urinary heparan sulphate derived glucosamine.

Coppa GV[1], Gabrielli O[1], Zampini L[1], Maccari F[2], Mantovani V[2], Galeazzi T[1], Santoro L[1], Padella L[1], Marchesiello RL[1], Galeotti F[2], Volpi N[3].

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Abstract

Mucopolysaccharidoses (MPS) are characterized by mental retardation constantly present in the severe forms of Hurler (MPS I), Hunter (MPS II) and Sanfilippo (MPS III) diseases.

On the contrary, mental retardation is absent in Morquio (MPS IV) and Maroteaux-Lamy (MPS VI) diseases and absent or only minimal in the attenuated forms of MPS I, II and III.

Considering that MPS patients affected by mental disease accumulate **heparan sulfate (HS)** due to specific enzymatic defects, we hypothesized a possible correlation between urinary HS-derived glucosamine (GlcN) accumulated in tissues and excreted in biological fluids and mental retardation. 83 healthy subjects were found to excrete HS in the form of fragments due to the activity of catabolic enzymes that are absent or impaired in MPS patients. On the contrary, urinary HS in 44 patients was observed to be composed of high molecular weight polymer and fragments of various lengths depending on MPS types. On this basis we correlated mental retardation with GlcN belonging to high and low molecular weight HS. **We demonstrate a positive relationship between the accumulation of high molecular weight HS and mental retardation in MPS severe compared to attenuated forms.** This is also supported by the consideration that accumulation of other GAGs different from HS, as in MPS IV and MPS VI, and low molecular weight HS fragments do not impact on central nervous system disease.

PLoS One. 2007 Aug 22;2(8):e772.

Development of sensory, motor and behavioral deficits in the murine model of Sanfilippo syndrome type B.

Heldermon CD[1], Hennig AK, Ohlemiller KK, Ogilvie JM, Herzog ED, Breidenbach A, Vogler C, Wozniak DF, Sands MS.

BACKGROUND:

Mucopolysaccharidosis (MPS) IIIB (Sanfilippo Syndrome type B) is caused by a deficiency in the lysosomal enzyme N-acetyl-glucosaminidase (Naglu). Children with MPS IIIB develop disturbances of sleep, activity levels, coordination, vision, hearing, and mental functioning culminating in early death. The murine model of MPS IIIB demonstrates lysosomal distention in multiple tissues, a shortened life span, and behavioral changes.

PRINCIPAL FINDINGS:

To more thoroughly assess MPS IIIB in mice, alterations in circadian rhythm, activity level, motor function, vision, and hearing were tested. The suprachiasmatic nucleus (SCN) developed pathologic changes and locomotor analysis showed that MPS IIIB mice start their daily activity later and have a lower proportion of activity during the night than wild-type controls. Rotarod assessment of motor function revealed a progressive inability to coordinate movement in a rocking paradigm. Purkinje cell counts were significantly reduced in the MPS IIIB animals compared to age matched controls. By electroretinography (ERG), MPS IIIB mice had a progressive decrease in the amplitude of the dark-adapted b-wave response. Corresponding pathology revealed shortening of the outer segments, thinning of the outer nuclear layer, and inclusions in the retinal pigmented epithelium. Auditory-evoked brainstem responses (ABR) demonstrated progressive hearing deficits consistent with the observed loss of hair cells in the inner ear and histologic abnormalities in the middle ear.

CONCLUSIONS/SIGNIFICANCE:

The mouse model of MPS IIIB has several quantifiable phenotypic alterations and is similar to the human disease. These physiologic and histologic changes provide insights into the progression of this disease and will serve as important parameters when evaluating various therapies.

Acta Neuropathol. 2008 May;115(5):547-59. Epub 2007 Dec 4.

Mechanisms of neurodegeneration in mucopolysaccharidoses II and IIIB: analysis of human brain tissue.

Hamano K[1], Hayashi M, Shioda K, Fukatsu R, Mizutani S.

Abstract

Mucopolysaccharidoses (MPS) are inherited disorders caused by the deficiency of lysosomal enzymes. Sanfilippo syndrome (MPS III) and Hunter syndrome (MPS II) are characterized by severe and mild neurological disorders, respectively, in which the neurodegenerative mechanisms remain to be clarified. We immunohistochemically examined the involvement of tauopathy/synucleinopathy, cell death and oxidative damage in the brains of three cases each of MPS IIIB and MPS II and age-matched controls. In cases of MPS IIIB, the density of GABAergic interneurons in the cerebral cortex immunoreactive for calbindin-D28K and parvalbumin was markedly reduced when compared with age-matched controls. The swollen neurons showed immunoreactivity for phosphorylated alpha-synuclein but not for phosphorylated tau protein or beta-amyloid protein; those in the cerebral cortex demonstrated nuclear immunoreactivity for TUNEL, single-stranded DNA and 8-OHdG. Neither lipid peroxidation nor protein glycation was marked in MPS cases. **The expression levels of superoxide dismutases (Cu/ZnSOD and MnSOD) and glial glutamate transporters (EAAT1 and EAAT2) were reduced in two MPS II cases. The disturbance of GABAergic interneurons can be related to mental disturbance, while synucleinopathy and/or DNA impairment may be implicated in the neurodegeneration of swelling neurons due to storage materials in MPS IIIB cases.** These findings suggest the possibility of neuroprotective therapies other than enzyme replacement in MPS patients.

J Neuropathol Exp Neurol. 1999 Aug;58(8):815-24.

Accumulation of intracellular amyloid-beta peptide (A beta 1-40) in mucopolysaccharidosis brains.

Ginsberg SD[1], Galvin JE, Lee VM, Rorke LB, Dickson DW, Wolfe JH, Jones MZ, Trojanowski JQ.

Abstract

To evaluate whether in vivo accumulations of heparan sulfate caused by inborn errors in the metabolism of glycosaminoglycans lead to the formation of neurofibrillary tangles and/or senile plaques, as seen in Alzheimer disease (AD), we studied postmortem brains from 9 patients, ages 1 to 42 years, with mucopolysaccharidosis (MPS). The brains of patients with Hurler's syndrome (MPS I: n = 5) and Sanfilippo's syndrome (MPS III; n = 4) as well as from caprine MPS IIID and murine MPS VII models were evaluated by thioflavine-S staining and by immunohistochemistry using antibodies directed against heparan sulfate proteoglycans, hyperphosphorylated tau, amyloid-beta peptide precursor proteins (APP), and amyloid-beta peptides (A beta [1-40], and A beta [1-42]). A two-site sandwich enzyme-linked immunosorbent assay (ELISA) was also utilized to compare levels of total soluble and insoluble A beta (1-40) and A beta (1-42) obtained from temporal cortex of MPS patients. Although no neurofibrillary tangles, senile plaques, or tau-positive lesions were detected in any of the MPS brains studied here, antibodies directed against A beta (1-40) intensely and diffusely stained the cytoplasm of cells throughout the brains of the MPS patients and the caprine MPS model. The ELISA assay also demonstrated a significant 3-fold increase in the level of soluble A beta (1-40) in the MPS brains compared with normal control brains. Thus, **at least some of the metabolic defects that lead to accumulations of glycosaminoglycans in MPS also are associated with an increase in immunoreactive A beta (1-40) within the cytoplasmic compartment where they could contribute to the dysfunction and death of affected cells in these disorders, but not induce the formation of plaques and tangles.** Models of MPS may enable mechanistic studies of the role A beta and glycosaminoglycans play in the amyloidosis that is a neuropathological feature of AD.

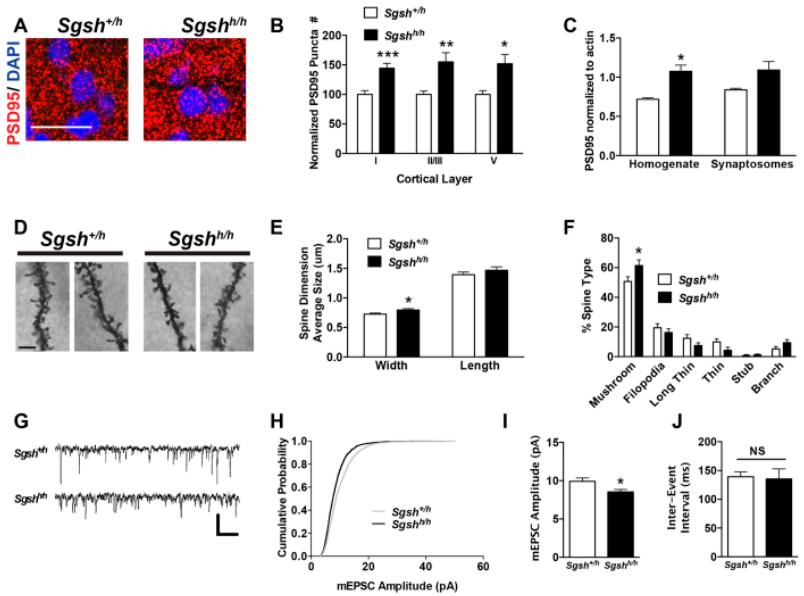
- Carpal tunnel syndrome and other entrapment neuropathy are very frequent in MPS, up to 50% of patients .
- Median nerve compression occurs as a result of thickening of the flexor retinaculum and the tissues around the tendon sheaths .
- Trigger digits are another very common feature of MPS.
- If carpal tunnel syndrome and trigger fingers are frequent in the healthy adult population and may seem ordinary, the physician should however be particularly careful in front of these pathologies occurring in children or young adults. Furthermore, the association of these two pathologies in the same patient is well recognized as a characteristic of patients with an MPS

Sci Rep. 2017 Apr 18;7:46576. doi: 10.1038/srep46576.

Neurodevelopmental Changes in Excitatory Synaptic Structure and Function in the Cerebral Cortex of Sanfilippo Syndrome IIIA Mice.

Dwyer CA[1], Scudder SL[2], Lin Y[1], Dozier LE[2], Phan D[1], Allen NJ[3], Patrick GN[2], Esko JD[1].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5394534/bin/srep46576-f1.jpgSanfilippo syndrome, MPS IIIA-D, results from deficits in lysosomal enzymes that specifically degrade heparan sulfate, a sulfated glycosaminoglycan. The accumulation of heparan sulfate results in neurological symptoms, culminating in extensive neurodegeneration and early death. To study the impact of storage in postnatal neurodevelopment, we examined murine models of MPS IIIA, which lack the enzyme sulfamidase. We show that changes occur in excitatory postsynaptic structure and function in the somatosensory cortex prior to signs of neurodegeneration. These changes coincide with accumulation of heparan sulfate with characteristic non-reducing ends, which is present at birth in the mutant mice. Accumulation of heparan sulfate was also detected in primary cultures of cortical neural cells, especially astrocytes. Accumulation of heparan sulfate in cultured astrocytes corresponded with augmented extracellular heparan sulfate and glypican 4 levels. **Heparan sulfate from the cerebral cortex of MPS IIIA mice showed enhanced ability to increase glutamate AMPA receptor subunits at the cell surface of wild type neurons. These data support the idea that abnormalities in heparan sulfate content and distribution contribute to alterations in postsynaptic function.** Our findings identify a disease-induced developmental phenotype that temporally overlaps with the onset of behavioral changes in a mouse model of MPS IIIA.



Clinical symptoms of MPS III

- **Somatic symptoms** in humans can include coarse facial features with broad eyebrows, dark eyelashes, dry and rough hair, and skeletal pathology that affects growth and causes degenerative joint disease, hepatosplenomegaly, macrocrania, and hearing loss.
- **The primary characteristic of MPS III is however degeneration of the central nervous system (CNS), resulting in mental retardation and hyperactivity, typically commencing during childhood, although there is some heterogeneity with respect to severity and age of onset.**
- Pre-natal and early stages of post-natal development are usually normal. The initial **stages of disease may begin between the ages of 1 and 3 years, which manifest as delayed cognitive development and/or aggressive behavioral problems, as well as hindered speech development.**
- **Behavioral difficulties may become increasingly severe between the ages of 3 and 5 years, commonly manifesting as a combination of hyperactivity, which is often violent and destructive, as well as sleep disturbances.**
- Patients may remain in this state for between 5 and 10 years, after which there is a **regression in behavioral disturbances**. This is associated with a **progressive and severe loss of intellectual processes (such as speech) and motor functions (including walking and swallowing).** MPS III patients ultimately regress to **a vegetative state until death**, which can occur anywhere between the early teens in the most severe scenarios, to as late as the sixth decade in attenuated forms.

Orphanet J Rare Dis. 2013 Dec 6;8:189. doi: 10.1186/1750-1172-8-189.

Natural history of Sanfilippo syndrome in Spain.

Delgadillo V[1], O'Callaghan Mdel M, Gort L, Coll MJ, Pineda M.

BACKGROUND:
Mucopolysaccharidosis type III (MPS III), or Sanfilippo syndrome, is caused by a deficiency in one of the four enzymes involved in the lysosomal degradation of heparan sulphate. Four MPS III types have been recognized, characterized by a large phenotypic heterogeneity. This is the first Spanish study describing the natural history of Sanfilippo patients (MPSIIIA, MPSIIIB and MPSIIIC), representing an essential step for understanding patient prognosis and for the establishment and application of future therapies.

METHODS:
This retrospective study aimed to establish the natural history of MPS III in Spain based on an extensive chronological data survey involving physicians and parents of 55 Spanish MPSIII patients. In addition to clinical description we report biochemical and molecular analysis already performed in the majority of cases.

RESULTS:
The most frequent subtype was MPS IIIA (62%). Symptoms before diagnosis were speech delay in 85%, followed by coarse facial features in 78%, and hyperactivity in 65% of cases at a mean age of 3 years old. The median age at clinical and biochemical diagnosis for each MPS III subtype were as follows: IIIA 4.4 years (1.2 - 16 years), IIIB 3.1 years (1-29 years), and IIIC 6.3 years (3.4-22 years).45% of patients developed epilepsy at a median age of 8.7 (2.5 - 37) years old.Age of death for MPS IIIA patients was 15 years (11.5 - 26 years).Molecular analysis of our cohort reveals, as alluded to above, a great allelic heterogeneity in the three subtypes without clear genotype-phenotype correlations in most cases.

CONCLUSION:
MPS IIIA is the most frequent subtype in Spanish Sanfilippo patients. Diagnosing physicians should consider Sanfilippo syndrome in children with non-specific speech delay, behavioural abnormalities, and/or mild dysmorphic features. We stress the importance of establishing early diagnosis procedures as soon as possible so as to be able to determine future short-term enzymatic or gene therapy treatments that can change the prognosis of the disease.

Classification of the MPS III phenotypes

Subtype	Phenotype MIM number	Activity	EC number	Gene/locus	Gene/locus MIM number	Cytogenetic location
MPS IIIA	MIM 252900	Sulfamidase	EC 3.10.1.1	*SGSH*	MIM 605270	17q25.3
MPS IIIB	MIM 252920	α-*N*-acetylglucosaminidase	EC 3.2.1.50	*NAGLU*	MIM 609701	17q21.1
MPS IIIC	MIM 252930	Heparan acetyl CoA: α-glucosaminide *N*-acetyltransferase	EC 2.3.1.78	*HGSNAT*	MIM 610453	8p11.1
MPS IIID	MIM 252940	*N*-acetylglucosamine 6-sulfatase	EC 3.1.6.14	*GNS*	MIM 607664	12q14.4
MPS IIIE	NA	*N*-glucosamine 3-*O*-sulfatase	EC 3.1.6.-	*ARSG*	MIM 610008	17q24.2

Notes: MPS IIIE is currently a proposed disease insofar as ARSG deficiency in humans has yet to be uncovered. As such, it has not been assigned an MIM number for its phenotype. The EC number for *N*-glucosamine 3-*O*-sulfatase has not been updated beyond 3.1.6.

Abbreviations: MIM, Mendelian Inheritance in Man; NA, not applicable; EC, Enzyme Commission; MPS, mucopolysaccharidosis; NAGLU, α-*N*-acetylglucosaminidase; HGSNAT, heparan acetyl CoA: α-glucosaminide *N*-acetyltransferase; GNS, *N*-acetylglucosamine 6-sulfatase; ARSG, arylsulfatase G; SGSH, N-sulfoglucosamine sulfohydrolase.

Am J Med Genet C Semin Med Genet. 2007 Aug 15;145C(3):293-301.

Is Sanfilippo type B in your mind when you see adults with mental retardation and behavioral problems?

Moog U[1], van Mierlo I, van Schrojenstein Lantman-de Valk HM, Spaapen L, Maaskant MA, Curfs LM.

Abstract

Sanfilippo type B is an autosomal recessive mucopolysaccharidosis (MPS IIIB) caused by deficiency of N-acetyl-alpha-D-glucosaminidase, a lysosomal enzyme involved in the degradation of heparan sulfate. It is characterized by neurologic degeneration, behavioral problems, and mental decline. Somatic features are relatively mild and patients with this disorder can reach late adulthood. It is the most common subtype of MPS in the Netherlands and probably underdiagnosed in adult persons with mental retardation (MR). In order to increase knowledge on the adult phenotype and natural history in Sanfilippo type B, we present the clinical data of 20 patients with this disorder. Sixteen of them were followed for one to three decades. Six died between 28 and 69 years of age, mainly from pneumonia and cachexia; the surviving patients were 18-63 years old. Apart from the youngest, they had lost mobility at 36-68 years. Most had developed physical problems, in particular in the 4th-6th decade of life: cardiac disease (cardiomyopathy, atrial fibrillations), arthritis, skin blistering, swallowing difficulties requiring feeding by a gastrostomy tube, and **seizures**. **The course of the disease was dominated in most of them by challenging behavioral problems with restlessness, extreme screaming and hitting, difficult to prevent or to treat pharmaceutically.** Even in absence of knowledge of the history of an elderly patient with MR, the presence of behavioral problems should prompt metabolic investigation for MPS.

Ital J Neurol Sci. 1981 May;2(2):119-27.

Sanfilippo A syndrome (mucopolysaccharidosis III A): a neurochemical study.

Federico A, Robert J, Zanetta JP, Guazzi GC.

Acta Neurol (Napoli). 1978 Jan-Feb;33(1):52-7.

Cerebral choline acetyltransferase and acetylcholinesterase activities in a Sanfilippo syndrome, in a myoclonic epilepsy and in various zones of the human newborn brain.

Federico A, Bartoccioni E, Massarelli R.

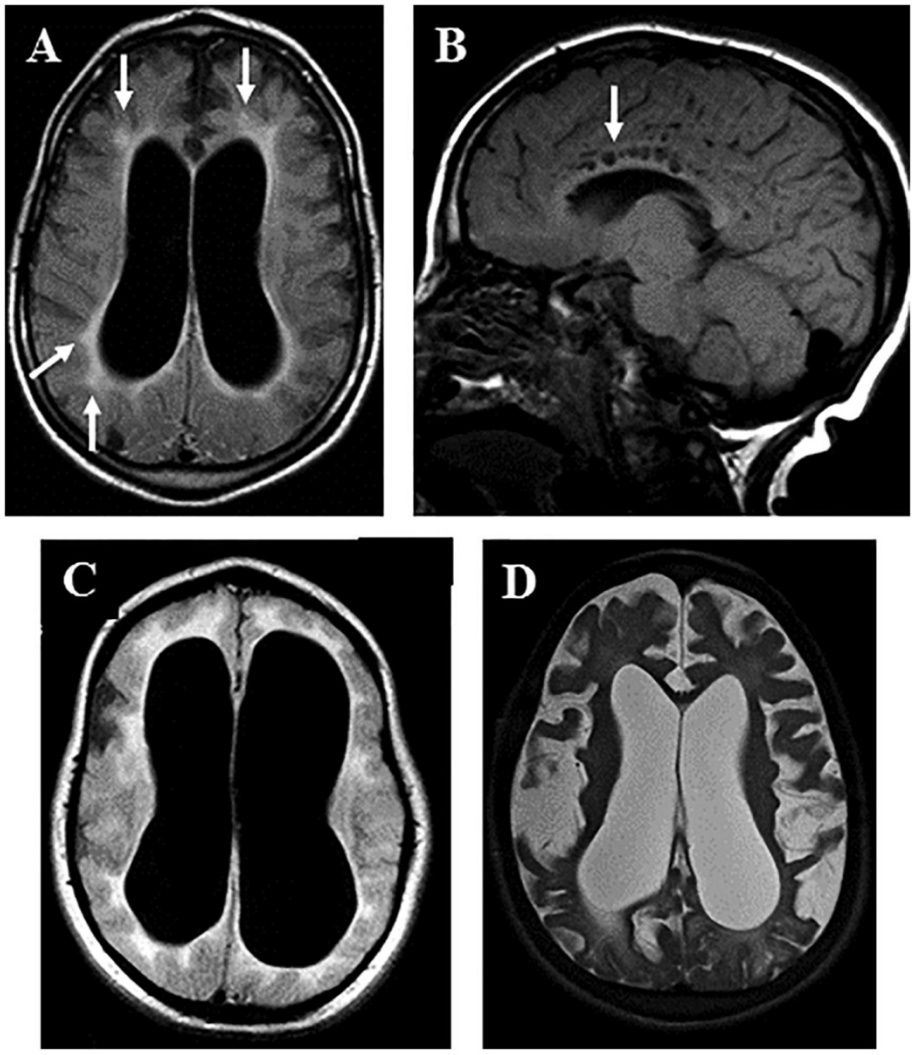
J Neurol. 1981;225(2):77-83.

Sanfilippo B syndrome (MPS III B): case report with analysis of CSF mucopolysaccharides and conjunctival biopsy.

Federico A, Capece G, Cecio A, D'Auria N, Di Iorio G, Ronsisvalle L, Di Natale P.

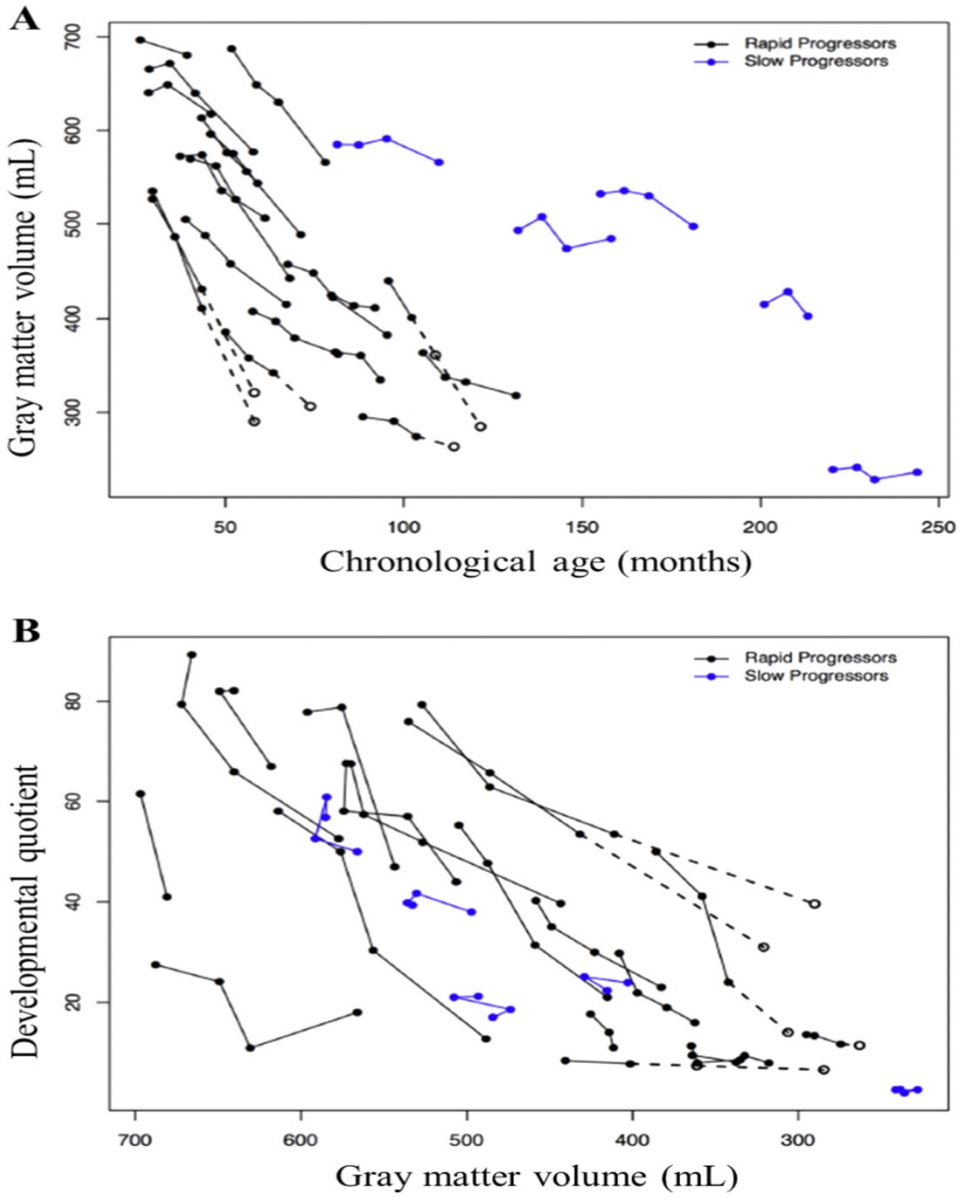
Abstract

A case of a child with Sanfilippo B syndrome (MPS III B), born of a consanguineous marriage, is reported. Urinary mucopolysaccharide analysis showed an abnormal excretion mainly of heparan sulphate. N-acetyl-a-glucosaminidase activity was absent in the patient but was present in the heterozygous range in parents and siblings. **CSF mucopolysaccharides were also abnormally high. In fibrocytes from conjunctival biopsy and CSF cells numerous vacuoles containing** storage material were found. The presence of vacuoles in fibrocytes from conjunctival biopsy and/or in CSF cells can be useful in the diagnosis of many suspected lysosomal storage disorders.



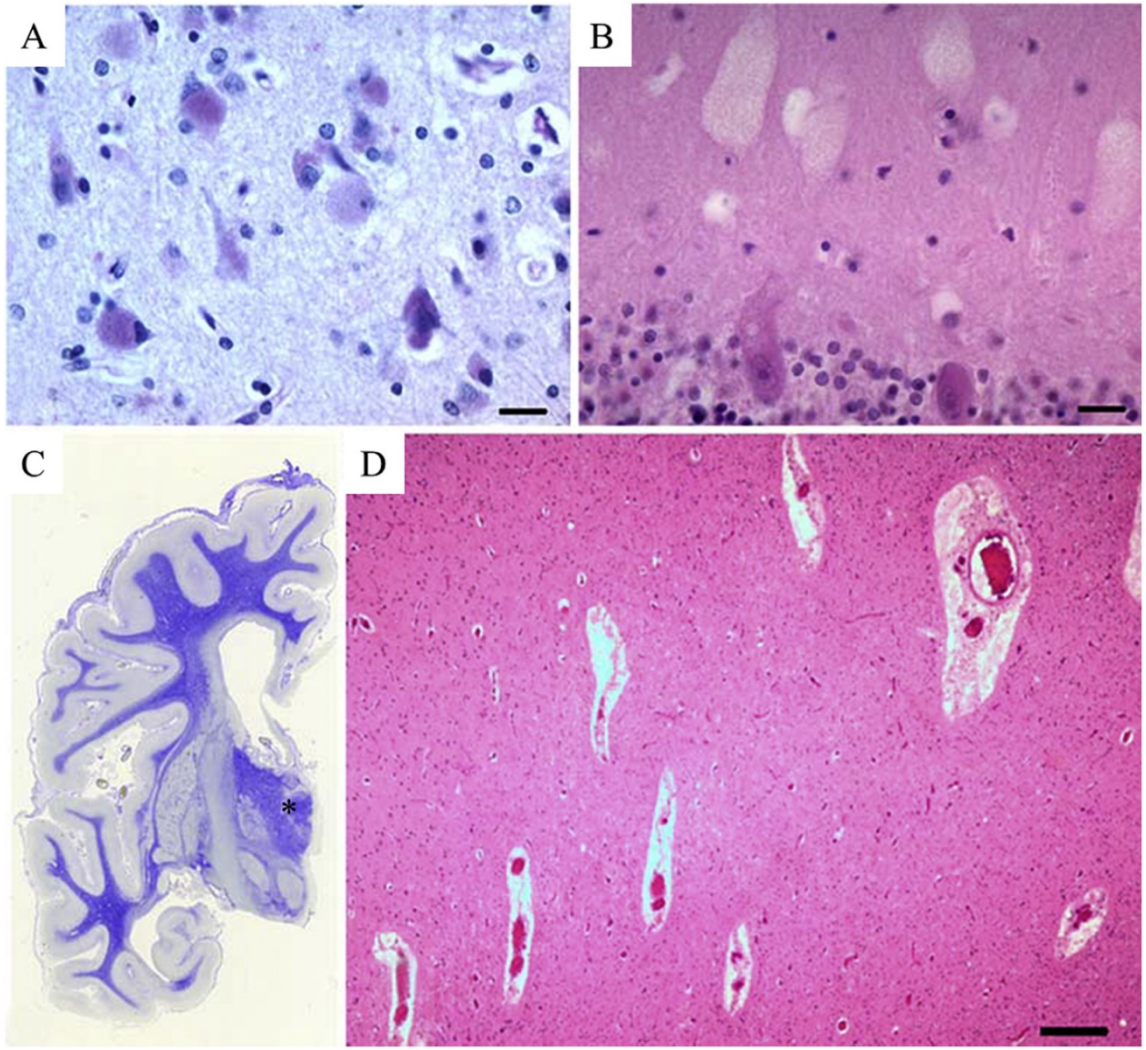
Anatomical changes in the brain of MPS patients: (A) moderate white matter lesions in the periventricular white matter (arrows) and moderate ventriculomegaly; (B) enlarged perivascular spaces in the corpus callosum (arrow); (C) hydrocephalus; (D) brain atrophy (Reproduced from Nestrasil & Vedolin, 2017 [33] with permission from Elsevier).

Molecular Genetics and Metabolism DOI: (10.1016/j.ymgme.2018.08.003)



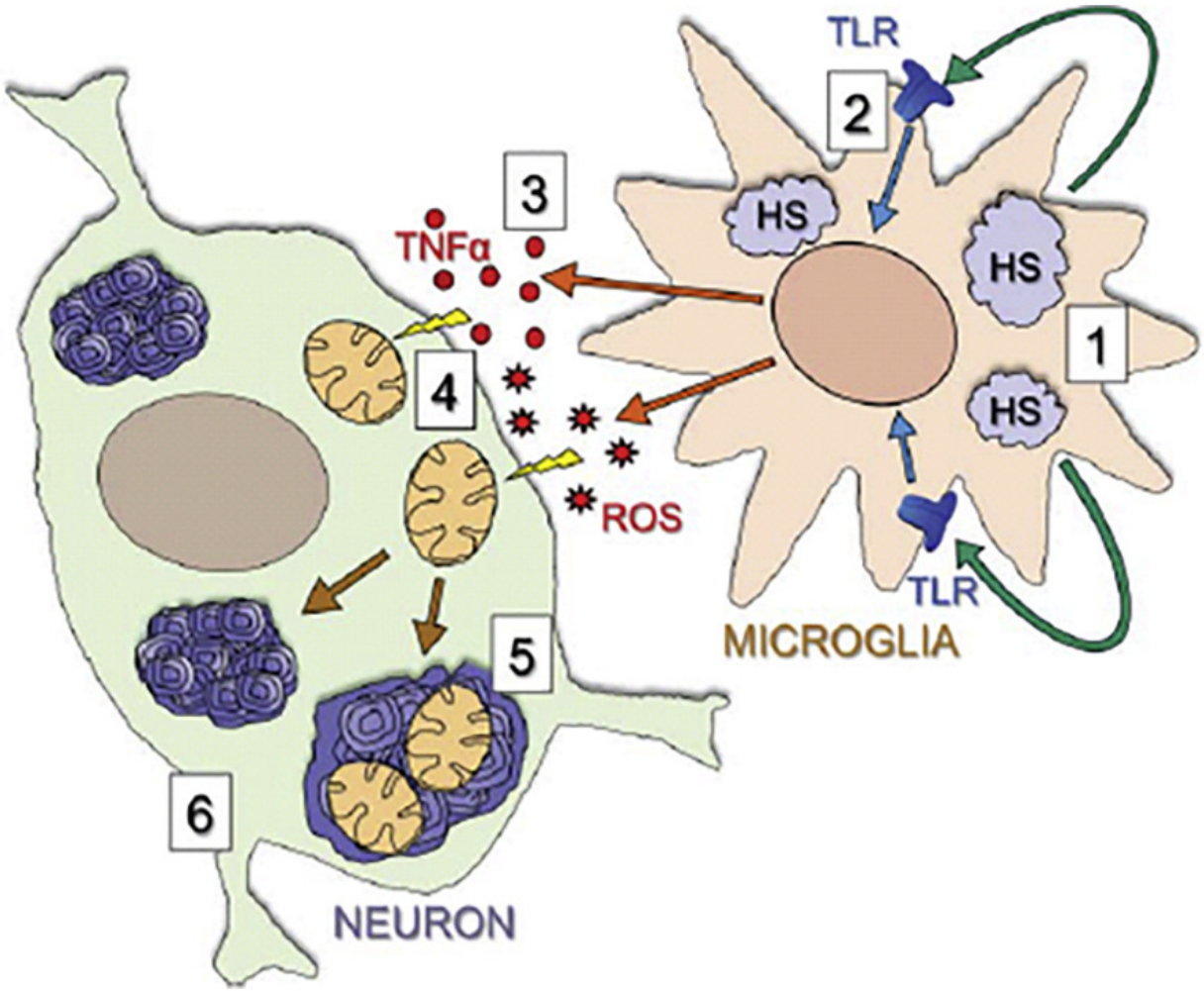
A) Gray matter volume reduces more rapidly in MPS IIIA patients with a fast decline ("fast progressors") in cognition/developmental quotient than in patients with a slow decline ("slow progressors"); B) The decline in developmental quotient correlates with gray matter volume reduction (reproduced from Shapiro et al. [31], with permission from Elsevier). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Quantitative neuroimaging in mucopolysaccharidoses clinical trials . Igor Nestrasil, Leonardo Vedolin Molecular Genetics and Metabolism Volume 122, Pages 17-24 (December 2017) DOI: 10.1016/j.ymgme.2017.09.006



Characteristic neuropathological changes in the brain of MPS patients with CNS involvement. (A) Neuronal swelling in the cerebral cortex, (B) dendritic swelling of Purkinje cells in the cerebellum, and (C) fibrous gliosis in the thalamus of MPS IIIB patients (asterisk). (D) Dilatation of the PVS in the white matter of an MPS II patient (Reproduced from Hamano et al., 2008 [3] with permission from Springer Science+Business Media).

A: periodic acid-Schiff staining; B and D: hematoxylin and eosin staining; C: Holzer staining. Scale bar in A and B = 20 µm; scale bar in D = 200 µm. CNS: central nervous system; MPS: mucopolysaccharidosis; PVS: periventricular space.



Proposed mechanism underlying CNS involvement in MPS IIIC mice. 1) **Accumulation of HS and HS-derived oligosaccharides accumulate in microglial cells**. 2) Release of this material triggers 3) a TLR-induced inflammatory response. 4) The inflammatory mediators cause mitochondrial damage and, 5) together with the primary storage, block autophagy, and lead to accumulation of gangliosides and misfolded proteins in the neurons, 6) which finally trigger neuronal cell death. (Reproduced from Pshezhetsky et al., 2015 [90] with permission from Taylor & Francis).

CNS: central nervous system; HS: heparan sulfate; MPS: mucopolysaccharidosis; ROS: reactive oxygen species; TLR: toll-like receptor; TNFα: tumor necrosis factor alpha.

Brian W. Bigger, David J. Begley, Daniela Virgintino, Alexey V. Pshezhetsky
Molecular Genetics and Metabolism DOI:
(10.1016/j.ymgme.2018.08.003)

Un caso clinico di MPS II diagnosticato a 39 anni!!!!!

E’ possibile ancora oggi?

Za… Carlo, nato nel 1979: nato pretermine (36esima settima), con parto distocico, gravidanza normocondotta, sofferenza neonatale per stress respiratorio e cianosi.
All'età di sei mesi, veniva ricoverato presso la U.O. Pediatria di Chieti per il episodi ricorrenti di iperpiressia di ndd, effettuava mielobiopsia negativa per leucemia.

Quadro complesso caratterizzato da macro-scafocefalia, collo corto, osteodistrofia congenita, rigidità articolare, scoliosi, gibbo dorsale, coxa-vara bilateralmente, camptodattilia, anemia ipocromica microcitica, epatosplenomegalia, rinite mucopurulenta cronica (agenesia dei seni frontali e sfenoidali, pansinusopatia cronica), ipoacusia mista bilaterale (aplasia del condotto uditivo esterno, alterazioni morfostrutturali della catena ossiculare, stenosi tubarica). Operato negli anni per tre ernie.

Visitato in molti importanti centri nazionali.
Ipotesi diagnostiche:
Malattia di Thiesman-Blailshord
Sindrome di Apert

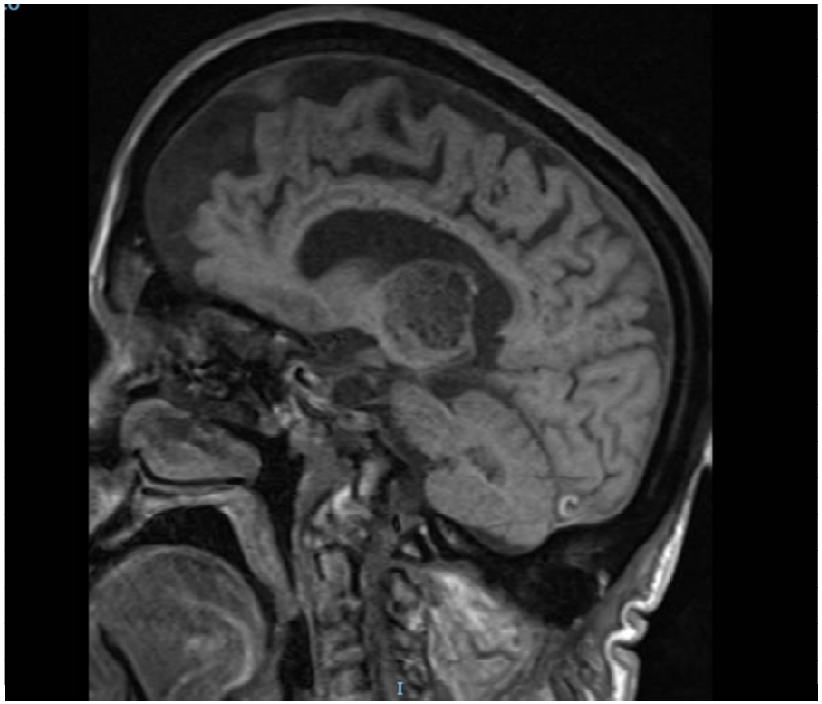
- **RM encefalo** ripetute nel tempo che mostrano **ipoindensità della sostanza bianca periventricolare, sottocorticale fronto-parieto-occipitale bilateralmente e mesencefalica, rigonfiamento dei talami che improntano i ventricoli laterali, atrofia fronto-temporale, assottigliamento del corpo calloso;**
- **EEG** (3/2/2016): nei limiti;
- **potenziali evocati acustici**: rallentamento della conduzione nervosa sulla via acustica bilaterale, distalmente ai nuclei cocleari;
- **ENG AASS**: **neuropatia dei nervi ulnare e mediano bilateralmente.**

Il quadro clinico nel tempo si è mantenuto sostanzialmente stabile; il paziente ha un alto livello di scolarità (laurea in scienze politiche) e lavora nell'azienda di famiglia.

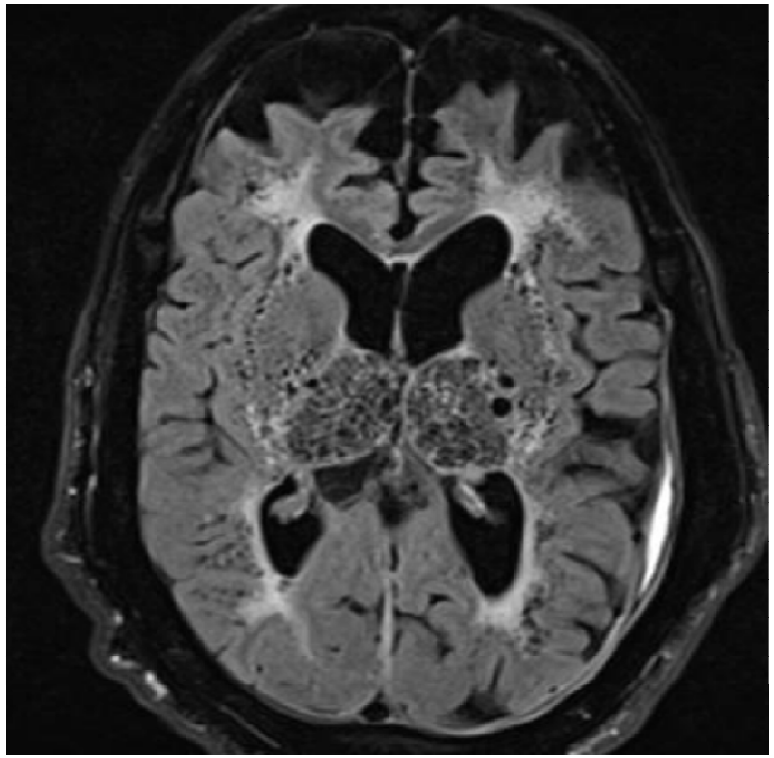
Nell'ultimo periodo comparsa di disturbo della deambulazione di tipo **atassico e significativa instabilità posturale.** Nei primi giorni di marzo, caduta a terra con contusione al quadricipite e all'anca a sinistra, dolore trattato con antifiammatori.

Ricovero nella nostra struttura a 38 anni:
Es: neurologico: andatura atassica, modesta dismetria ed adiadoconinesia, macrocefalia, macroglossia, facies gargoilica, ipoacusia, osteodistrofia con mani ad artiglio.
Veniva sottoposto ai seguenti accertamenti:

- **dosaggio mucopolisaccardi urinari:** significativamente aumentati.
- **dosaggio attività enzimatica di alfa-L-iduronidasi (MPSI):** attività enzimatica nella norma.
- **dosaggio attività enzimatica di iduronato-2-solfatasi (MPSII):** 0.77 nmol/4h/mg (v.n. 18-57) su leucociti del sangue periferico; 3075 (v.n. 165-475) su plasma. L'attività enzimatica media è risultata ridotta su pellet di leucociti e su plasma rispetto ai controllo normali rispettivamente al 2% e 1,12%. Tale risultato è compatibile con la diagnosi di Mucopolisaccaridosi di tipo 2.
- **striscio di sangue periferico:** alcuni leucociti con inclusioni eosinofile.



Sagittale T1: macrocrania, deformazione della sella turcica, marcata atrofia diffusa con consensuale idrocefalo, notevole assottigliamento del corpo calloso. Falda di ematoma subdurale cronico fronto parietale (traumatico)



Trasversale FLAIR: diffuso ampliamento da accumulo degli spazi periventricolari con aspetto cribroso particolarmente evidente nei talami e nella sostanza bianca biemisferica e marcata reazione gliotica adiacente.

Analisi genetico-molecolare del gene della iduronato 2 solfato solfatasi

Ia variante c.253 G>C, rilevata nell'esone 3 del gene IDS, è stata precedentemente descritta come patogenica da Cooper et al. Altre varianti missenso sono state descritte nella stessa posizione aminoacidica per tale residuo una importanza nella funzionalità della proteina: p Ala85Thr (c.253.G>A) da Rathmann et al. ed altri autori. La variante è considerata patogenetica (classe 1) secondo le raccomandazioni di Centogene dell'ACMG.

CENTOGENE
THE RARE DISEASE COMPANY

Am. J. Hum. Genet. 59:1202–1209, 1996

Mucopolysaccharidosis Type II (Hunter Syndrome): Mutation "Hot Spots" in the Iduronate-2-Sulfatase Gene

Michaela Rathmann,[1] Susanna Bunge,[1] Michael Beck,[2] Hans Kresse,[3] Anna Tylki-Szymanska,[4] and Andreas Gal[1]

[1]Institut für Humangenetik, Universitäts-Krankenhaus Eppendorf, Hamburg; [2]Kinderklinik der Universität, Mainz; [3]Institut für Physiologische Chemie der Universität, Münster; and [4]Department of Metabolic Diseases, Child Health Centre, Warsaw

J Inherit Metab Dis (2013) 36:179–187
DOI 10.1007/s10545-012-9533-7

ORIGINAL ARTICLE

Molecular characterization of 355 mucopolysaccharidosis patients reveals 104 novel mutations

Laura M. Pollard · Julie R. Jones · Tim C. Wood

- **RX scheletro in toto:** in assenza di precedenti esami non forniti, in riferita diagnosi di mucopolisaccaridosi di tipo 2,si conferma come rilevato nella TC precedente, un netto ispessimento sclerotico della teca cranica. Scoliosi ad S dorso-lombare con netta curvatura cifotica con fulcro in D12 che appare nettamente deformato a cuneo anteriore. Modesta spondilosi dei metameri dorso-lombari che presentano irregolarità delle limitanti somatiche come da presenza di piccole ernie intraspongiose. Netta deformazione dell'epifisi prossimali di entrambi i femori con netta riduzione di ampiezza delle interlinee articolari coxo-femorali e disomogeneità osteostrutturali di entrambe le teste femorali. A carico dell'emipiatto tibiale esterno di entrambe le ginocchia si evidenziano lacune ossee pluriloculate con orletto sclerotico (formazioni geodiche?). In atteggiamento flesso obbligato delle dite di entrambe le mani ,si evidenzia irregolarità e deformazione dei capi ossei dei polsi e a livello metacarpo-falangeo con ampliamento delle interlinee articolari sia dei polsi che delle mani.

- **Rx rachide con studio dinamico:** L'esame, corredato da proiezioni dinamiche, mostra regolare allineamento dei metameri.

- **TC rachide:** Indagine eseguita da C2 a D2. Perdita della fisiologica lordosi del rachide cervicale con antiversione della curva con fulcro C5-C6. Spessore dei corpi somatici ridotto da C2 a D2 con deformazione a lente biconvessa. Ai confini dello studio si rileva uno spiccato ispessimento con segni di osteoclerosi della diploe dell'osso occipitale.

- **TC torace:** ispessimento delle pareti bronchiali nel LSD con evidenza di secrezioni endoluminali e micronoduli centrolobulari da patologia flogistica delle piccole viee aeree; concomitano a ridosso dei segmenti apicale e posteriore del LSD alcune lesioni escavate delimitate da una spessa parete, la maggiore delle quali delle dimensioni di 30x23 mm circa mostra componente densa declive. Lesione focale ipodensa di circa 1 cm tra VII e IV segmento epatico, in sede alta sottodiaframmatica. Posizione alta dell'emidiaframma di sin. Alterazioni delle limitanti somatiche contrapposte del rachide dorsale con cuneizzazione di D12 associata a fenomeni erosivi del rispettivo muro somatico anteriore.

- **Consulenza pneumologica:** paziente affetto da MPS2 a causa della quale è presente, oltre alle altre manifestazioni neurologiche e muscolo-cheletriche, rinite muco purulenta cronica e agenesia dei seni frontali, sfenoidali e pansinusopatia cronica. Dal punto di vista respiratorio il paziente riferisce dispnea da sforzo e tosse modestamente produttiva, senza però a riuscire ad espettorare. E' forte russatore ed il padre che lo accompagna riferisce di aver notato apnee da sonno. E.O.: SpO2 in aria ambiente 98%, FC 48-52 bpm, PA 90/60 mmHg. All'ascoltazione del torace è presente una riduzione del MV su tutto l'ambito polmonare e ronchi scarsamente modificabili con la tosse. Non sono presenti edemi declivi agli arti inferiori ma riferisce che saltuariamente l'edema è presente. Le prove di funzionalità respiratoria, per quanto possibile a causa delle limitazioni fisiche del paziente, mostrano quadro di restrizione. Non è stato possibile eseguire studio pletismografico e determinazione della diffusione alveolo-polmonare. L'EGA in aria ambiente mostra ipercapnia con compenso metabolico renale.

- **Il paziente inizia terapia con enzima ricombinante con buona tolleranza.**
- **Le condizioni respiratorie peggiorano notevolmente, con un grave episodio di edema polmonare, perdita della coscienza, grave insufficienza respiratoria, trauma cranico con ematoma subdurale.**
- **Ricovero in Rianimazione e decesso dopo 15 gg.**

Mol Genet Metab. 2017 Jun;121(2):138-149. doi: 10.1016/j.ymgme.2017.04.004. Epub 2017 Apr 9.

Efficacy of laronidase therapy in patients with mucopolysaccharidosis type I who initiated enzyme replacement therapy in adult age. A systematic review and meta-analysis.

Pérez-López J[1], Morales-Conejo M[2], López-Rodríguez M[3], Hermida-Ameijeiras Á[4], Moltó-Abad M[5].

BACKGROUND:

The efficacy of starting enzyme replacement therapy (ERT) in adults with Muchopolysaccharidosis Type I (MPS-I) is controversial. Evaluating the benefits reported by patients initiating ERT with laronidase at adult age might help physicians decide whether the use of ERT in these patients is worthwhile from a clinical point of view.

OBJECTIVE:

To assess every effectiveness variable modified in MPS-I patients who initiated laronidase at adult age.

METHODS:

A systematic search of the literature, from inception to July 2016, was conducted using MEDLINE, EMBASE, CENTRAL and LILACS to identify randomized trials or observational studies including ≥1 MPS-I patients with ERT initiated in adult age (≥18years) and evaluating ERT efficacy. A meta-analysis of studies evaluating the same effectiveness outcome was performed and the evidence was rated according to GRADE criteria. Heterogeneity was assessed by the Chi-squared test and the I-squared statistic. Case reports were excluded from meta-analysis but their main outcomes were separately evaluated. The decrease in urine glycosaminoglycans (uGAGs) levels as patient percentage with reduction in uGAGs and with normalization was the primary outcome.

RESULTS:

Nineteen clinical studies and 12 case reports were selected. ERT decreased uGAG levels (high evidence) and liver volume (high), improved 6-min walking test (6MWT) (moderate) and increased blood anti-ERT antibody levels (high). There was no conclusive results (low or very low evidence) regarding improvement/stabilization of respiratory function, change in shoulder flexion, cardiac improvement/stabilization, improvement in symptoms of nocturnal hypoventilation and sleep apnea, improvement in quality of life, visual acuity, otolaryngologic function, bone mineral density or effectiveness of intrathecal therapy.

LIMITATIONS:

Excluding case reports, there was no study conducted specifically in the target population (ERT ≥18years). Data were from subgroup analyses of selected studies. There was a great heterogeneity between designs and clinical outcomes evaluated.

CONCLUSIONS:

ERT improves uGAGs and liver volume in MPS-I patients initiating therapy as adults, although the putative clinical benefit associated to these improvements is unclear. Moderate evidence was shown for improvement in 6MWT. Systematic review registration number (PROSPERO): 42,016,041,306.

Orphanet J Rare Dis. 2016 Apr 26;11:50. doi: 10.1186/s13023-016-0425-z.

Severe tracheal and bronchial collapse in adults with type II mucopolysaccharidosis.

Rutten M[1], Ciet P[2,3], van den Biggelaar R[1], Oussoren E[4], Langendonk JG[4,5], van der Ploeg AT[4], Langeveld M[6,7].

BACKGROUND:

Mucopolysaccharidosis type II (MPSII) patients frequently suffer from dyspnoea caused by restrictive airway disease due to skeletal abnormalities as well as glycosaminoglycans (GAG) accumulation at different levels of the airway, including the trachea. In this study we describe the extent of the tracheal and bronchial narrowing, the changes in airway diameter during respiration and the effects of these obstructions on respiratory function in adult MPSII patients.

METHODS:

Five adult MPSII patients (mean age 40 years) were included. Pulmonary function tests and in- and expiratory chest CT scans were obtained. Cross-sectional areas of trachea and main bronchi were measured at end-inspiration and -expiration and percentage collapse was calculated.

RESULTS:

There was diffuse narrowing of the entire intra-thoracic trachea and main bronchi and severe expiratory collapse of the trachea in all patients. At 1 cm above the aortic arch the median % collapse of the trachea was 68 (range 60 to 77%), at the level of the aortic arch 64 (range 21-93%), for the main bronchi this was 58 (range 26-66%) on the left and 44 (range 9-76%) on the right side. The pulmonary function tests showed that this airway collapse results in obstructive airway disease in all patients, which was severe (forced expiratory volume <50% of predicted) in four out of five patients.

CONCLUSION:

In adult MPS II patients, central airways diameters are strikingly reduced and upon expiration there is extensive collapse of the trachea and main bronchi. This central airways obstruction explains the severe respiratory symptoms in MPSII patients.

Mol Genet Metab. 2017 Jun;121(2):70-79. doi: 10.1016/j.ymgme.2017.05.004. Epub 2017 May 6.

Cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses: Results of a consensus procedure.

van der Lee JH[1], Morton J[2], Adams HR[3], Clarke L[4], Ebbink BJ[5], Escolar ML[6], Giugliani R[7], Harmatz P[8], Hogan M[9], Jones S[10], Kearney S[11], Muenzer J[12], Rust S[13], Semrud-Clikeman M[14], Wijburg FA[15], Yu ZF[16], Janzen D[17], Shapiro E[18].

Author information

Abstract

The design and conduct of clinical studies to evaluate the effects of novel therapies on central nervous system manifestations in children with neuronopathic mucopolysaccharidoses is challenging. Owing to the rarity of these disorders, multinational studies are often needed to recruit enough patients to provide meaningful data and statistical power. This can make the consistent collection of reliable data across study sites difficult. To address these challenges, an International MPS Consensus Conference for Cognitive Endpoints was convened to discuss approaches for evaluating cognitive and adaptive function in patients with mucopolysaccharidoses. The goal was to develop a consensus on best practice for the design and conduct of clinical studies investigating novel therapies for these conditions, with particular focus on the most appropriate outcome measures for cognitive function and adaptive behavior. The outcomes from the consensus panel discussion are reported here.

- **The MPS disorders are caused by deficiencies in enzymes involved in GAG catabolism, leading to growth retardation and progressive damage to respiratory, cardiovascular, musculoskeletal, nervous, gastrointestinal, auditory, and visual systems.**
- **Better methods for diagnosis, multi-disciplinary care, and new therapies have extended lifespan, leading to an increasing number of adults with MPS.**

Optimal care for adults with MPS requires:

- **Programs guiding transition from pediatric to adult health care**
- **Continuation of routine evaluations of clinical manifestations throughout adulthood**
- **A medical home or coordinating physicians who can monitor disease progression and streamline disease management**
- **Management teams composed of health care specialists properly trained to meet the specific, unique, medical needs of adult MPS patients**
- **Development of adult rare disease clinics and inclusion of treatable rare diseases into training programs in adult medicine**
- **More studies focusing on adult MPS patients**

The study of rare diseases: butterfly collecting or an entrèe to understanding common conditions?

K. Talbot

Pract. Neurol. 7: 210-211, 2007

"Nature is nowhere accustommed more openly to display her secret mysteres than in cases where she shows traces after working apart from the beathen path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discoveries of the usual law of nature by careful investigation of causes of rarer forms of diseases. For it has been found, in almost all things, that what they contain of useful or applicable is hardly preceived under we are deprived of them or they become deranged in some way".

William Harvey, 1647