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### RESEARCH ARTICLE

#### SEVERE HUNTER DISEASE: ABOUT A CASE

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#### Abstract

Hunter's disease is a rare genetic disorder caused by the abnormal buildup of compounds called glycoaminoglycans (or mucopolysaccharides) in body cells. There is a range of clinical forms ranging from severe forms (type A), with early intellectual impairment, to moderate forms (type B) with little or no intellectual impact. Its prognosis is reserved given the notion of multisystemic failure. The diagnosis is based on the dosage of high urinary glycosaminoglycans and the dosage of the collapsed iduronate-2-sulfatase activity. Brain magnetic resonance imaging allows early detection of lesions indicative of cranial damage. Management is based on enzyme replacement therapy and on hematopoietic stem cell transplantation. It delays clinical manifestations and improves the quality of life for patients. We report the case of a boy with this pathology in his severe form.

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#### Introduction:-

Hunter's disease is a rare metabolic pathology secondary to an enzyme deficiency responsible for an accumulation of glycosaminoglycans (1; 2). It mainly affects males (2; 3; 4). This accumulation occurs mainly in the bones and joints, ears, lungs and heart and generally causes deafness, short stature, heart problems, joint pain.

The diagnosis of this pathology is confirmed by a high level of urinary glycosaminoglycans and a collapsed level of iduronate-2-sulfatase.

Magnetic resonance imaging remains necessary for better detection of brain damage in the severe form of Hunter's disease.

There is no specific treatment to cure this disease, however multidisciplinary management is essential for the treatment of symptoms and the correction of the enzyme deficiency iduronate-2-sulfatase.

#### Patient and Observation:-

It is about a 5 years old boy, without family pathological history, presented about a year a heart failure, a deformation of the fingers in claw, gait disturbances, associated with a macrocrania with a regression of psychomotor acquisitions and behavioral disorders.

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Biological assessment revealed a high level of urinary mucopolysaccharides and the collapse of the activity of iduronate-2-sulfatase confirming the diagnosis of Hunter's disease  
Cerebro-medullary magnetic resonance imaging revealed active-type hydrocephalus with enlarged cortical grooves indicating atrophy (Figure a) associated with dorso-lumbar scoliosis (Figure d).

The patient underwent a ventriculo-peritoneal shunt to treat hydrocephalus. It is combined with an enzyme replacement therapy every week by infusion throughout the life of our patient.

The post-therapeutic follow-up was marked by an improvement in the regression of cardiac signs with an improvement in motor skills, however the child still had behavioral and intellectual disorders.

**Discussion:-**

Hunter's disease is a rare and orphan disease; mucopolysaccharidosis (type II), which has more or less severe forms (2; 4). Mucopolysaccharidoses are lysosomal genetic diseases. Hunter's disease mainly affects males. It is X-linked gonosomal recessive inheritance. Its incidence is around 1 / 80,000 boy births.

**Pathophysiology:**

Hunter's disease is a genetic disease that is one of the diseases known as "lysosomal overload". This means that certain compounds, which are normally eliminated or recycled by the body, are not broken down and accumulate in the bones and joints, the ears, the lungs and the heart.

These compounds, called mucopolysaccharides, are normally broken down into small bags called lysosomes, found in each cell. This is because lysosomes contain substances called enzymes, which normally break down mucopolysaccharides into small molecules that can be reused by the cell. However, in Hunter's disease, one of these enzymes, iduronate-2-sulfatase, is abnormal. Consequently, the breakdown of mucopolysaccharides and their evacuation out of cells is not carried out correctly. These accumulate in lysosomes and become toxic to cells.

The manifestations of the disease depend on the amount of mucopolysaccharides accumulated and on the part of the body where they accumulate (bones, heart, brain...).

Babies are not sick at birth, but as their cells store waste products, symptoms appear (8). Depending on the severity of the genetic anomaly and therefore the severity of the dysfunction of the enzyme iduronate2-sulfatase which results (total absence or partial functioning), the symptoms are more or less severe and concern more or less organs.

**Moderate clinical forms (type B):**

Moderate forms of Hunter's disease is very variable. The signs are not very marked. They appear later in childhood or adolescence and evolve more slowly. At first, intelligence is normal throughout life, although there may be some learning difficulties. The main manifestations are joint stiffness, progressive hearing loss and heart problems with retained neurological function. In this moderate form, the patients live until adulthood, sometimes even up to 50 years for the least severely affected.

**Severe clinical forms (type A):**

These forms of the disease are much more severe because the brain is affected. Most often, the child shows no particular sign at birth. The first manifestations appear during the first year of life and then gradually increase to become more marked around two years of age.

Facial dysmorphism becomes typical between 9 months and 2 years of age, associated with macrocephaly: the features are coarse, the nose widened, the nasal saddle marked, the eyes protruding, the swollen eyelids; there is often protruding macroglossia and thickening of the lips, gums, ears, skin; gingival enlargement which causes the child to keep their mouth open all the time.

**Osteo-articular involvement:**

A statural advance is usual during the first 2 years of life then appears a break in statural growth with a maximum size less than 1.10 m. Short-radius thoracolumbar kyphosis was noted when the seated station was acquired. Gradually, the joints of the hand deform and the fingers assume a contracted position, in "claw."

Short radius thoracolumbar kyphosis was noted when the seated station was acquired. Joint stiffness due to multiple dysostosis gradually sets in. Femoral and acetabular dysplasia with coxa valga can lead to hip dislocation (9). Bone radiographs show characteristic multiple dysostosis.

**Digestive damage:**

The abdomen is prominent with hepatosplenomegaly (12), umbilical and inguinal hernias, often bilateral or recurrent in a non-premature infant. Abdominal pain, diarrhea and / or chronic constipation are common

**Cardio-vascular injury:**

Cardiovascular involvement includes thickening of the valves, cardiomyopathy with arrhythmia, development of pulmonary hypertension, sometimes coronary artery disease (10). Progressive infiltration of the pulmonary interstitium, stiffness and antero-superior crushing of the costal grill lead to respiratory failure (13).

**Brain damage:**

Cerebral damage manifests itself firstly by a delay in motor acquisition: postural insufficiency with delay in acquisition of head holding in the most severe forms, or more often of free sitting, then of walking which can be embarrassed by an equine or equine varus of the feet; habitual lack of cleanliness, language delay aggravated by otolaryngology and sensory problems, with behavioral problems.

**Neuro-orthopedic involvement:**

Neuro-orthopedic manifestations are frequent: bilateral carpal tunnel syndrome responsible for dysesthesia or pain, particularly at night, then thenar amyotrophy and muscle weakness (11); cervical or spinal cord compression at the thoracolumbar junction, very rarely instability, even atlanto-axoid dislocation; a sensory impairment gradually sets in. Deafness is first transmissive then perceptual. Progressive corneal opacities cause photophobia and then loss of uncorrectable visual acuity. Glaucoma, retinopathy, optic atrophy can occur during evolution. Tri- or tetra-ventricular hydrocephalus per gene for resorption of cerebrospinal fluid linked to infiltration of the meninges worsens the neurological state but is accessible to neurosurgical treatment. Progressive psychomotor regression leads to severe mental retardation, and to a bedridden state with progressive loss of all cognitive and motor brain functions.

**Imaging:**

Cerebral MRI early shows multiple deep pseudo-lacunar images, which appear to be located in the white matter but in fact correspond to a dilation of the perivascular spaces of VirchowRobin, also observed in the attenuated forms [6]. There may also be white matter signal anomalies predominantly periventricular and in the oval centers suggesting myelin damage [5; 6]. There gradually appears a dilation of the subarachnoid spaces and ventricles by cortico-subcortical atrophy.

**Diagnostic:**

The final diagnosis is generally only obtained between the ages of 2 and 4 years. Faced with a strong suspicion of hunter's disease, there are two ways either by a high level of urinary glycosaminoglycans or a collapsed level of iduronate-2-sulfatase.

**Differential diagnosis:**

Hunter's disease can be confused with other lysosomal diseases, including other mucopolysaccharidoses (types I and VI).

**Evolution:**

The course obviously depends on the severity of the disease. Children with Hunter's type A disease have severe symptoms that worsen over time. The course is different from one child to another, but in adolescence, the vast majority of children with severe form can no longer walk, are very thin and weak, with an abnormal contraction of the muscles of the body (7). Their life expectancy is greatly reduced, with death generally occurring before or at the start of adulthood. Conversely, people with type B disease do not have intellectual regression and their life expectancy can be extended.

**Therapeutic care:****Specific treatment:**

Consists to improve patients' quality of life by treating symptoms and correcting the enzyme iduronate-2-sulfatase deficiency. Enzyme replacement therapy by idursulfase (name of the substitute enzyme) helps restore a sufficient level of enzyme activity to partially degrade the waste accumulated in the patient's cells.

However, the enzyme does not reach the brain, and therefore does not repair already existing neurological damage.

**Symptomatic treatment:**

The progressive nature of Hunter's disease requires regular clinical and paraclinical evaluation to best adapt symptomatic treatment and prevent certain visceral and orthopedic complications: physiotherapy, occupational therapy, psychomotor therapy, devices. Surgical treatments include: hernia repair, surgery for osteoarticular or spinal deformity, carpal tunnel release, spinal cord compression surgery and / or atlanto-axoid instability, ventriculo-peritoneal shunt in the event of hydrocephalus. Analgesic treatment can be difficult to assess and adapt due to behavioral and relationship disorders. The treatment of sleep disorders is firstly based on the treatment of pain and its cause (eg ear infections, dental caries, esophagitis, carpal tunnel syndrome, neuropathy, headache reflecting intracranial hypertension, etc.), without forgetting the appropriate treatment for sleep apnea.

**Conclusion:-**

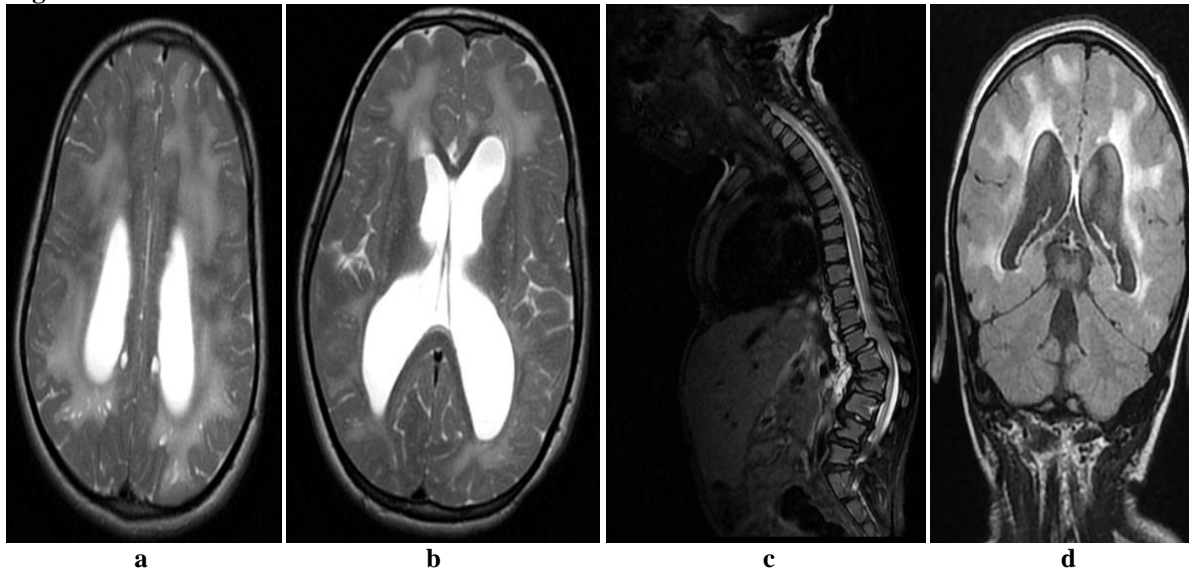
Hunter's disease is a rare lysosomal genetic disorder in which its severe form is common. Its prognosis is reserved given the notion of multisystemic failure. The diagnosis of certainty is biological. Management is based on enzyme replacement therapy and on hematopoietic stem cell transplantation. It delays clinical manifestations and improves the quality of life for patients.

**Conflicts Of Interest:**

The authors do not declare any conflict of interest.

**Contributions by Authors**

All the authors have contributed to this work. All authors have read and approved the final version of the manuscript.

**Legend:**

**Figure:-** Brain MRI in axial slices, coronal (a, b, c) and sagittal medulla (d) T2 without injection: highlights dilation of the perivascularial spaces of VirchowRobin, signal abnormalities of the white matter predominantly periventricular and at the level of oval centers with dilation of the ventricles and sub arachnoid spaces by cortico-subcortical atrophy associated with dorso-lumbar scoliosis.

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