Magnetic resonance imaging findings in Hunter syndrome

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Abstract

Hunter syndrome is a rare genetic lysosomal storage disease that is caused by a deficiency, or absence, of iduronate-2-sulphatase, an enzyme needed to break down specific glycosaminoglycans (GAGs). As a result, GAGs build up in various tissues throughout the body leading to adverse neurological and non-neurological effects. This literature review focuses on the neurological findings. Although few magnetic resonance imaging studies have been conducted, those done have shown that patients with Hunter syndrome generally exhibit brain atrophy, enlarged periventricular spaces and ventriculomegaly. Similar findings have been reported in other mucopolysaccharide disorders. Enzyme replacement therapy is a novel treatment which has had success in treating peripheral disease in mice and humans.

Conclusion: Future studies should focus on how structural and chemical signatures in the brain of Hunter patients are altered before and after enzyme replacement therapy, and how those alterations correlate with clinical outcome.

INTRODUCTION

Hunter syndrome (mucopolysaccharidosis type II, MPS II) is one of seven rare lysosomal storage diseases caused by a deficiency, or absence, of enzymes needed to breakdown and recycle specific glycosaminoglycans (GAGs) (formerly known as mucopolysaccharides) (1). Unlike the other mucopolysaccharide diseases, Hunter syndrome is a recessive X-linked disease and is caused by the congenital absence (or deficiency) of iduronate-2-sulphatase. Without iduronate-2-sulphatase, GAGs build up in the skeletal tissue, connective tissue and central nervous system (CNS), causing a range of symptoms and problematic health issues.

The disease is clinically characterized by coarse facial features, skeletal dysplasia, joint stiffness and limited mobility (1). Patients generally display hepatosplenomegaly as well as inguinal and umbilical hernias. The thickening of heart valves can eventually lead to cardiovascular failure, and the thickening of airway walls can lead to sleep apnoea, diminished lung capacity, obstructive airway disease and respiratory infections. Patients with the severe phenotype of the disorder usually show symptoms at a young age, around 2–4 years. They generally exhibit intellectual and social development and frequently survive into middle age (1,3,4).

NEUROLOGICAL FINDINGS: MRI AND HUNTER SYNDROME

Magnetic resonance imaging (MRI) can be an extremely useful tool for diagnosing and monitoring the pathological progression of diseases. However, to date, the study of Hunter syndrome with MRI has been very limited. Not enough research on this topic exists to define the characteristic appearance of the brain in Hunter syndrome (3). Nevertheless, a few generalized observations have been made: Hunter syndrome is neurologically characterized by abnormal changes detected on MRI; in particular, there is a ‘sieve-like’ appearance within periventricular and subcortical white matter (4–9) and in the basal ganglia (4,5,9,10) and corpus callosum (5,7,9). There is also significant regional atrophy (4–6). These findings indicate that the unique ability of MRI to differentiate between various tissues, specifically with the use of T1- and T2-weighting techniques, can be particularly helpful in following the pathological status of the disease (8). This paper will review case studies and reports that illustrate specific neurological findings in patients with Hunter syndrome. These findings are summarized in Table 1.

An MRI study conducted by Shimoda-Matsubayashi et al. (10) focused on a 44-year-old male with the typical mild form of MPS II. Increased and decreased signals in T1- and T2-weighted images gave rise to a ‘honeycomb-like’ appearance in the patient’s basal ganglia and thalamus, believed to be caused by the build up of glycolipids and GAGs, and increased fluid in the periventricular spaces (PVS). While previous research had shown increased signal density in the white matter of patients with severe MPS II (11,12), this was the first MRI study to report these particular results in a patient with the milder form of MPS II. Despite the observation of severe atrophy, along with other clear clinical manifestations of the disease (skeletal abnormalities, coarse facial features and short stature), the 44-year-old patient was mentally healthy. In addition, the patient showed no characteristic behaviour associated with basal ganglia or thalamic damage.
Table 1  Summary of brain magnetic resonance imaging findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>MPS disorder</th>
<th>Area of interest</th>
<th>Abnormal magnetic resonance results related to Hunter syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shimoda-Matsubayashi et al. (10)</td>
<td>One, 44-year-old man</td>
<td>MPS IIB</td>
<td>Brain</td>
<td>‘Honeycomb-like’ appearance in thalamus and basal ganglia; white matter abnormality</td>
</tr>
<tr>
<td>Kulkani et al. (11)</td>
<td>Eight</td>
<td>MPS IIA</td>
<td>Brain</td>
<td>Changes in the periventricular white matter</td>
</tr>
<tr>
<td>Nakajima et al. (12)</td>
<td>One</td>
<td>MPS IIA</td>
<td>Brain</td>
<td>Changes in the white matter</td>
</tr>
<tr>
<td>Shinomiya et al. (7)</td>
<td>One, 3-year-old boy</td>
<td>MPS IIB</td>
<td>Brain</td>
<td>Spindle-like areas in the white matter, including the corpus callosum; white matter showed high signal on T2-weighted images</td>
</tr>
<tr>
<td>Lee et al. (5)</td>
<td>14</td>
<td>Six with MPS IH; five with MPS II; three with MPS IIIA</td>
<td>Brain</td>
<td>Multiple cystic or sieve-like lesions (described as ‘cribriform’ changes) involving peri- and supraventricular, parietal, white matter, corpus callosum and basal ganglia, inversely related to degree of atrophy, ventricular enlargement and white matter changes</td>
</tr>
<tr>
<td>Parsons et al. (4)</td>
<td>Five</td>
<td>MPS IIB</td>
<td>Brain, neck and cervical spine</td>
<td>Atrophy, grey and white matter signal changes (particularly in the thalamus, basal ganglia and PVS), ventriculomegaly</td>
</tr>
<tr>
<td>Okane et al. (8)</td>
<td>Two boys, a 15-year-old and a 3-year-old</td>
<td>MPS IIA</td>
<td>Brain</td>
<td>Enlargement of the lateral ventricles and third ventricle. Cerebral cortical sulci were diffusely dilated. Abnormal intensity lesions in the lateral part of the thalamus, the subcortex of the insula, the pons, and the right thalamus. Diffuse hypointensity throughout the periventricular white matter. In Case 2, numerous hypointense spots in the corpus callosum and the cerebral white matter. Multiple cystic changes. Numerous linear hypointense lesions. Patchy areas of hypointensity in the parietal lobes</td>
</tr>
<tr>
<td>Matheus et al. (6)</td>
<td>18</td>
<td>Six with MPS I and 12 with MPS IIB</td>
<td>Brain</td>
<td>Abnormal periventricular white matter, widened cortical sulci, supratentorial ventricles and enlarged subarachnoid spaces</td>
</tr>
</tbody>
</table>

MPS, mucopolysaccharidosis; MPS IIA, severe form of MPS II; MPS IIB, mild form of MPS II; PVS, periventricular spaces.

A later study of a 3-year-old boy with the mild form of MPS II reported similar findings (7). The MRI revealed large ‘spindle-like’ areas of increased and decreased signal in the white matter and corpus callosum. In T2-weighted images, the white matter showed high signal, isointense with cerebrospinal fluid on all other pulse sequences. These neural abnormalities were believed to be caused by increased fluid and build up of glycolipids and GAGs. Again, no mental retardation was reported.

A larger project compared the MRI findings of five children with the severe form of MPS II, six with MPS IH (Hurler syndrome), and three with MPS IIIA (Sanfilippo A syndrome) (5). Most notably, unlike the previous studies, the children with Hunter and Hurler syndromes had the most severe multiple cystic or sieve-like lesions, which involved the peri- and supraventricular parietal white matter, the corpus callosum and the basal ganglia. The most severe sieve-like changes occurred in younger patients. These, so called, ‘cribriform’ changes were inversely related to the degree of atrophy, ventricular enlargement and white matter changes observed in the subjects. Although mental retardation was, as expected, most severe in children with Hurler and Hunter syndrome, the severity of retardation did not correlate with the severity of cribriform changes. In fact, the degree of mental retardation was correlated with the degree of atrophy, ventricular enlargement and white matter changes, as expected because of the loss of cerebral tissue. Based on these findings, the authors postulated that mucopolysaccharide disorders have a natural course in the brain: the multiple cystic or sieve-like lesions being followed by white matter changes, and finally by atrophy. According to this theory, optimal therapeutic intervention should take place at the time of, or before, the appearance of sieve-like changes.

Parsons et al. (4) conducted MRI studies on the brains, necks and cervical spines of five male patients (age range, 9–27 years) with the mild form of MPS II. The most prominent abnormalities were atrophy, grey and white matter signal changes (particularly in the thalamus, basal ganglia, brain stem and periventricular white matter) and ventriculomegaly (dilation of the lateral ventricles). The severity of the periventricular white matter changes did not correspond to age; however, increased atrophy and ventriculomegaly were both more prominent in older subjects. As described by Shimoda-Matsubayashi et al. (10), the ‘honeycomb-like’ pattern within the thalamus and basal ganglia was also observed in older patients. Like the previous findings, these results were attributed to the build up of GAGs. Four
of the five cases had spinal cord compression and narrowing of the upper airway due to increased tissue in the neck. Again, despite these brain and spine abnormalities, none of the five subjects were mentally retarded.

Another study of two patients, a 15-year-old boy and a 3-year-old boy, with the mild form of MPS II is consistent with the MRI findings of the studies above. The MRI results suggested abnormal tissue in the thalamus, dilated ventricles, hyperintensity through the periventricular white matter, and areas of hypointensity in the corpus collosum and white matter (8).

In a study of Hunter syndrome conducted in 2004, the MRI brain scans of 18 patients (aged 6–20 years), six with MPS I and 12 with the mild form of MPS II, were assessed retrospectively (6). The most commonly affected region was the periventricular white matter (14 out of 18 patients) (Fig. 1). However, subjects also exhibited widened cortical sulci, supratentorial ventricles and enlarged subarachnoid spaces (Fig. 2). Although previous studies have correlated atrophy with mental deterioration (1,13), this study had the same findings as others described in this paper. Despite somewhat severe brain atrophy and ventriculomegaly in 14 patients, none had mental retardation. Also, as in previous studies, there was no relationship between MRI abnormalities and clinical manifestations. The most notable finding in this particular study was that the enlarged PVS had the same signal intensity as cerebrospinal fluid (CSF) (Fig. 3). Previous research indicated that dilation of the PVS was due to GAG build up (14,15). However, this most recent study suggests that the dilation is caused by a malfunction in the mechanism to reabsorb CSF (6). All of the subjects studied had enlarged PVS, even those with no ventriculomegaly. This finding suggests that dilation of the PVS might impair the flow of normal CSF in the brain, and an enlarged PVS (seen on MRI) could be a good marker for abnormal CSF circulation, as well as progression of disease.

Recently, Vedolin et al. (16) reported on MRI and magnetic resonance spectroscopy (MRS) in 19 male patients with MPS II. Results from 12 patients with the severe
phenotype, which is associated with cognitive impairment, were compared with seven patients with the mild phenotype. Magnetic resonance studies found that subjects with cognitive impairment not only presented with more severe white matter lesions than those without, but more frequently showed evidence of brain atrophy and hydrocephalus. Spectroscopy results showed that the cognitively impaired subjects also had a higher myoinositol/creatine ratio in both the grey and white matter, compared with the cognitively unimpaired, mild phenotype subjects (Fig. 4). The authors speculate that myoinositol elevation could be a glial response to intraneuronal deposition of GAG, an increase in the volume of neuronal cells or an indirect marker of GAG deposition. This study successfully demonstrated that MRI and MRS can be used to determine the severity of brain compromise in patients with MPS II. Additionally, this study showed how the use of spectroscopy may provide crucial insight into the pathophysiology associated with GAG deposits.

In the largest and most recent study by Vedolin et al. (17), the influence of aging on MRI and MRS was investigated in 60 patients with MPS (31 with MPS II). The correlations between enzyme levels, urinary GAG and neuroimaging findings were also studied. For the first time, quantitative analysis of MRI variables was performed using both semi-automated and automated segmentation tools. This strategy was important to provide accurate, reproducible and quantitative measures for assessing imaging findings, such as brain atrophy, white matter lesion load and ventricular size. The authors found that patients with MPS II with longer disease duration had more white matter lesions and a lower mean cerebral volume. Also, MRI and MRS variables in either the white or the grey matter did not correlate with enzymatic activity or GAG levels. Regarding demographic data, two additional interesting findings were observed. First, in all patients, disease onset was before 7 years of age. Secondly, most patients had their first MRI examination at 10 years of age, rather late in the course of the disease.

A final longitudinal study used proton magnetic resonance spectroscopy (1H-MRS) to look at seven patients with different types of MPS (18). The primary goal of this study was to measure the cranial accumulation of mucopolysaccharides in patients with MPS disorders and to evaluate other potential biochemical abnormalities. In addition, 1H-MRS measurements were performed in two patients, pre- and post-bone marrow transplantation (BMT). Based on 1H-MRS spectra recorded in vitro from samples of chondroitin sulphate-C, dermatan sulphate and urine from patients with MPS disorders, a resonance at 3.7 ppm was considered to contain signals from mucopolysaccharides and labelled as presumptive mucopolysaccharides (pMPS). In general, differences in pMPS, choline and N-acetyl aspartate (NAA) levels were observed in patients with MPSs compared with healthy control subjects and, in one patient, altered metabolism was detected following BMT. These results suggest that 1H-MRS may provide useful biochemical information regarding the efficacy of BMT in patients with MPS. However, it should be noted that this study was performed using a relatively low magnetic field strength (1.5 Tesla). Due to low 1H-MRS spectral resolution, the assignment of the 3.7–4.1 ppm chemical shift region to pMPS is ambiguous and open to interpretation. Future studies may benefit from the use of higher magnetic field strengths coupled with more sophisticated 1H-MRS methods to assist pMPS identification and quantification in patients with MPS disorders.

OTHER FINDINGS
MRI has been used to study other body systems affected by Hunter syndrome (Table 2). A number of studies have
focused on the spinal cords of patients with Hunter syndrome, many of whom experience compression of the spinal cord caused by a thickening of the cervical meninges, posterior longitudinal ligament and dura mater due to GAG deposition (3,19,20). Other spinal abnormalities are: cervical instability, C1–C2 subluxation and compressive spondylolysis. These patients often present with fractured spines or intense neck pain.

A case study of a 15-year-old boy was done to examine a hip fracture he had suffered (21). In his case, build up of GAGs caused synovial thickening, pressure erosion of the femoral neck (which eventually led to the total absorption of the left femoral head) and a subsequent stress fracture. Magnetic resonance techniques were useful for discovering abnormal intra-articular soft tissues in both hips, which were identified by their low signal intensity on T1-weighted and T2-weighted sequences.

A rather interested study performed MRS on the urine of patients with MPS disorders to gather data on urinary GAG excretion (22). Subjects included patients with MPS types I, II, IIIA, IVA and VI. This study revealed that the molecular structures of specific excreted GAGs were distinct for the different types of MPS. For example, excreted keratan sulphate was directly linked to the patients with MPS IV (Morquio syndrome). Using this method, MRS could be useful in determining the exact type of MPS disorder.

### OTHER MPS DISORDERS

**MPS I**

MPS I is subdivided into three phenotypes based on severity: Hurler syndrome being the most severe, Hurler–Scheie syndrome, the moderate form of the disease, and Scheie syndrome being the mildest. All three phenotypes are caused by the absence or deficiency of the enzyme α-L-iduronidase. Of the other MPS disorders, it is clinically most like MPS II. Like MPS II, MPS I is also characterized by progressive white matter changes and ventricular enlargement from sieve-like changes, and the unexpected preservation of mental capacities (5,23).

**MPS III (Sanfilippo syndrome)**

MPS III is subdivided into four groups – A, B, C and D. The disorder is an autosomal recessive disease caused by failure to break down heparan sulphate. Each subtype is characterized by a deficiency in a specific enzyme in the heparan sulphate degradation pathway (24). The disorder is marked by severe neurological symptoms (25). Also like MPS I and II, patients with Sanfilippo syndrome have some ventricular enlargement and white matter changes (5).

**MPS IV (Morquio syndrome)**

MPS IV, like other forms of MPS, has two subtypes: type A and type B. This particular form of MPS results from an inability to break down keratan sulphate, with subsequent accumulation of this GAG. Type A is marked by a deficiency in N-acetylgalactosamine-6-sulphate sulphatase (GALNS), and type B is caused by a deficiency in the enzyme β-galactosidase. Both GALNS and β-galactosidase are necessary for the breakdown of keratan sulphate (26). MPS IV is a form of dwarfism, and symptoms can include systemic bone dysplasia, respiratory problems, hearing loss and cataracts. One MRI study found thickened dura mater at the cranio-cervical junction, spinal cord compression and white matter alterations (27).

**MPS VI (Maroteaux–Lamy syndrome)**

MPS VI is a rare and fatal lysosomal storage disease. Often, this disorder has no effective treatment, although for some patients bone marrow transplant is a viable option (28), and for others, enzyme replacement therapy (ERT) can have positive effects (6). MPS VI results from a deficiency in arylsulphatase B (29). Few MRI data exist, but some noteworthy findings have been the following: a dilation in the PVS, spinal cord compression (30), compression at the cranio-cervical junction (31) and white matter changes (32).

**MPS VII (Sly syndrome)**

MPS VII has many similar symptoms to Hurler syndrome. However, in this case, the metabolic disorder is characterized by a deficiency in the enzyme β-glucuronidase. MRI findings are similar to MPS VI (30).

**MPS IX (Natowicz syndrome)**

MPS IX comes from a deficiency in hyaluronidase. Its symptoms are similar to the other MPS diseases (33), but it is characterized by the build up of hyaluronan (34). Currently, no MRI data exist on this disorder.
DISCUSSION

As stated above, most of the brain imaging findings in Hunter syndrome demonstrate changes or differences in the brain when compared with healthy individuals. In the study conducted by Vedolin et al. (16) the severity of brain abnormality signified by the magnetic resonance results correlated with the cognitive impairment of the subjects. However, oddly enough, in most studies described, there was little connection between imaging data and clinical manifestations of the disease (6). While these findings are of interest, it is clear that relatively little research has been conducted using MRI to look at Hunter syndrome, evidenced by the limited number of publications exploring this topic, and even within those publications, the small sample sizes utilized.

One of the drawbacks of such limited data is that it is still unclear if any of the reported brain abnormalities can really be considered as ‘markers’ for the disease. The current results may not be sufficient simply because similar MRI findings have been seen in other disorders. The three most consistent brain differences found in MPS II are considered hallmarks of other diseases, or at the very least have been documented in them: atrophy, enlarged PVS and ventriculomegaly.

Atrophy, which is the shrinking or wasting away of the brain, seems to be the most prevalent MRI finding in Hunter syndrome. Atrophy is a classic sign associated with Alzheimer’s disease and, in the elderly, atrophy is associated with mental decline. However, patients with the mild form of MPS II, who present with brain atrophy similar to that observed in patients with Alzheimer’s disease, do not demonstrate comparable cognitive deficits. Those with Alzheimer’s disease have shown global brain atrophy, as well as atrophy in the frontal region, temporal region, hippocampus, amygdala and the right cerebellum (35,36). Global brain atrophy has also been seen in younger patients with multiple sclerosis (37,38), and reduced volumes of the caudate, putamen and cerebellum have been reported in juvenile Huntington disease (39).

Enlarged PVS have also been found in the elderly and those suffering from dementia (40). In particular, dilated PVS have been seen in the frontal and parietal white matter (41), that are extremely similar to the enlarged PVS seen in patients with Hunter syndrome. Dilatation of the PVS has also been seen in patients with Sotos syndrome (42), although the MRI findings in Sotos syndrome are considered distinctive (43), whereas the MRI findings for MPS II are not.

Ventriculomegaly (dilation of the lateral ventricles) has been seen in a wide variety of disorders. Like enlarged PVS, it has also been seen in Sotos syndrome (42). It has also been documented in cerebral palsy (44) and Prader–Willi syndrome (45), and is common after severe head trauma (46).

Despite this overlap with other conditions, there appear to be characteristic differences in the brains of patients with the MPS disorders. For example, none of the conditions mentioned above (i.e. Alzheimer’s disease, Sotos syndrome, Prader–Willi syndrome and multiple sclerosis) report a ‘honeycomb-like’ or ‘sieve-like’ appearance in any part of the brain. Three studies all reported this same appearance in the corpus callosum, thalamus and basal ganglia, respectively (5,7,10), but these findings are also reported in other MPS disorders (9). In addition, Matheus et al. (6) reported dilation in the basal ganglia and thalamus and, although they did not report a ‘honeycomb-like’ appearance, the MRI images (see Fig. 2) look similar to those of Shimoda-Matsubayashi et al. (10). Matheus et al. (6) questioned whether the structural differences seen in the brains of patients with Hunter syndrome were due to increased CSF or GAG build up. However, if the observed structural changes are indeed a result of GAG build up (as much of the other literature suggests), and therefore a marker of MPS disorders, more targeted therapies could be implemented.

ERT has been effective in treating peripheral disease associated with MPS in mice (47,48), and Muenzer et al. (2) similarly found success in treating peripheral disease in human patients with MPS II. Future research, looking at MRI scans before and after ERT, to see if the development of the ‘honeycomb-like’ appearance can be slowed down or reversed, might shed more light on the disease and its course in the brain. Likewise, if more MRS research were conducted, perhaps specific chemicals (choline/creatine or N-acetyl aspartate/creatine) could be studied to see the effects of ERT on those spectra.

CONFLICT OF INTERESTS STATEMENT

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All remaining authors declare no conflict of interests.

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