The challenges of diagnosing patients with an ultra-rare disease – insights from the European MPS VII study

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Background

- It is estimated that there are only around 30 patients with a confirmed diagnosis of MPS VII in Europe
- In common with other ultra-rare diseases, it can take several years to arrive at a diagnosis
- Earlier diagnosis is necessary to achieve the best outcomes for patients as enzyme replacement therapy becomes available

What is MPS VII?

Mucopolysaccharidosis VII (or Sly disease) is an ultra-rare metabolic condition characterised by the deficiency of ß-glucuronidase.

Lack of this enzyme leads to accumulation of ß-glycosaminoglycans, causing cellular and organ damage.

Disease severity and life expectancy can vary greatly between individuals.

In some it presents as non-immune hydrops fetalis (NIHF) and can lead to death *in utero*, or death in the early weeks of life.

Children that survive can develop short stature, skeletal dysplasia, hepatosplenomegaly, hernias, cardiac involvement, pulmonary insufficiency and cognitive impairment.

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Methods

- The study was designed and co-ordinated by MPS Commercial, UK
- Patient organisations and other professional contacts from 25 countries were asked if they were aware of any individuals with MPS VII
- Local patient organisations and clinicians supported the study by contacting their MPS VII families
- Informed consent was obtained from all participants before completion of a specifically designed and translated questionnaire

Acknowledgements

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Results

- A total of 18 individuals were identified, of which 13 consented to take part in the study
- The individuals were from Germany (n=2), Spain (n=3), The Netherlands (n=2) and Turkey (n=6)
- Individuals with MPS VII ranged in age from 3 to 34 years (mean 17.1 years), two were siblings
- All questionnaires were completed by the individual with MPS VII's parent or carer

What led to a diagnosis of MPS VII

For most individuals, diagnosis was a result of the development of symptoms (53.8%) or presentation with NIHF (30.8%). One child was diagnosed due to diagnosis of MPS VII in a sibling and one family reported that it was due to 'the insistence of the parents that the child was different.'

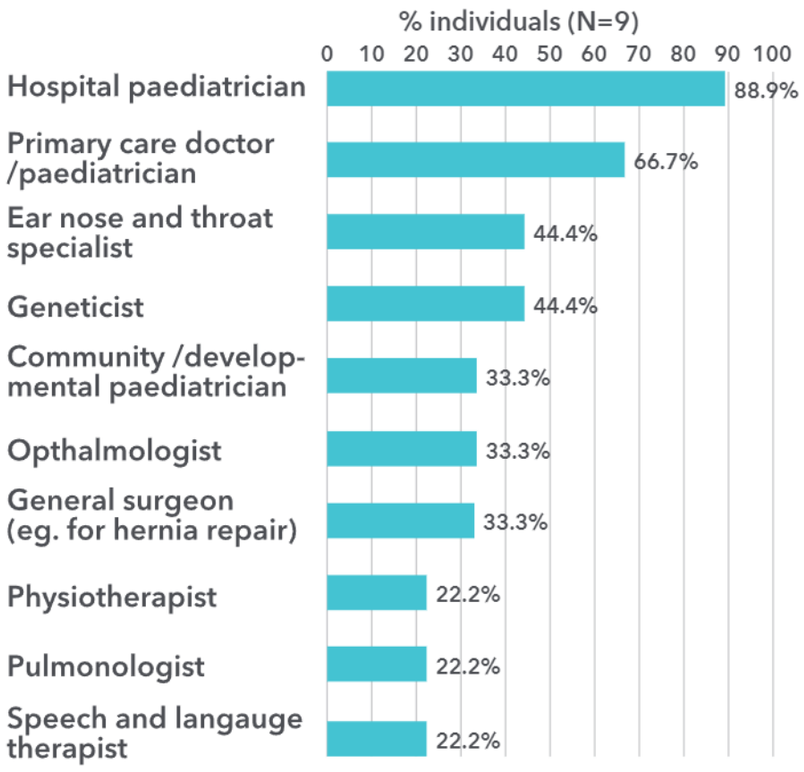
Age at diagnosis

- Overall, 38.5% of individuals had presented with NIHF, and this led to testing and diagnosis of MPS VII in all but one of these children
- Children with NIHF were diagnosed at a mean age of 1.9 years (range 0–6 years, n=5)
- Those without NIHF were diagnosed at a mean age of 5.3 years (range 0–14 years, n=8)

Diagnostic journey for those not diagnosed due to the presence of NIHF

- Most individuals were seen by more than one type of healthcare professional (HCP) before diagnosis (mean 4.6 professionals)
- The most frequently seen HCPs are shown in Figure 1

Figure 1. Most commonly consulted HCP's before diagnosis of MPS VII



Two-thirds of individuals had received a prior diagnosis, the most common were attention deficit hyperactivity disorder, autistic spectrum disorder and Perthes disease (all 22.2%, N=9).

By the time they were diagnosed, these children had displayed a wide range of symptoms (Table 1).

Table 1. Combination of symptoms present before diagnosis per individual (N=9)

AGE AT DIAGNOSIS (YEARS)	Birth–2			3–6			7–14		
SUBJECT	1	2	3	4	5	6	7	8	9
NIHF	*				✓				
Difficulty with toilet training				✓	✓	✓	✓	✓	
Unusual eating habits			✓			✓	✓		✓
Recurrent constipation							✓		
Chronic nasal discharge				✓		✓	✓	✓	
Recurrent respiratory infections				✓	✓			✓	✓
Noisy breathing				✓			✓		✓
Snoring					✓		✓		✓
Recurrent ear infections				✓	✓	✓	✓		✓
Problems with hearing				✓	✓		✓		
Dental problems		✓					✓		
Corneal clouding	✓				✓				
Sleep disturbance		✓		✓	✓	✓		✓	✓
Sleep apnoea							✓		✓
Challenging behaviour	✓		✓		✓	✓	✓	✓	
Hyperactivity					✓	✓		✓	
Repetitive behaviour	✓					✓	✓	✓	
Suspected or diagnosed autistic spectrum disorder						✓		✓	
Coarse facial features / dysmorphology	✓	✓	✓	✓	✓	✓	✓	✓	✓
Thick hair /eyebrows	✓	✓	✓	✓	✓		✓		✓
Large head		✓	✓	✓	✓		✓		
Large tongue				✓	✓				
Large stomach					✓				✓
Enlarged liver and / or spleen	✓		✓	✓	✓		✓		✓
Heart problems	✓			✓					
Hernia, bulging of abdominal wall around umbilicus or groin		✓	✓	✓	✓		✓	✓	✓
Epilepsy, absences, fits or seizures							✓		
Joint stiffness or pain	✓		✓	✓	✓		✓		✓
Delayed walking		✓		*	✓		✓		✓
Loss of walking ability previously acquired					✓				✓
Delayed speech				*	✓	✓	✓	✓	✓
Loss of speech previously acquired					✓				
Delayed learning				*	✓	✓	✓	✓	
Loss of learning previously acquired				✓			✓		

*unknown

Conclusions

- For children that do not present with NIHF, diagnosis can take several years
- Early symptoms can be non-specific and mistaken for other conditions
- It is hoped that studies of this nature will support the earlier recognition of symptoms and disease characteristics associated with MPS diseases