

Prevalence of intestinal disease as terminal event in Mucopolysaccharidosis Type III – A study of 136 deceased patients

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Background

Mucopolysaccharidosis III (MPS III; Sanfilippo syndrome) is an autosomal recessive lysosomal storage disorder primarily causing progressive neurological deterioration,¹ but other body systems can also be affected.²

The Society for Mucopolysaccharide Diseases (MPS Society, UK) was aware, through its work with patients and their families, that **individuals with MPS III have a wide range of gastrointestinal (GI) conditions**. This led to a multi-agency meeting between MPS Society and UK specialist clinics, which determined GI conditions are prevalent across all ages but have not usually caused major clinical concern.

Longevity of MPS III patients has increased over the last decades² and GI symptoms may become more troublesome with age. It is unclear if they are a complication from prescribed treatments for GI symptoms, e.g. laxatives or antidiarrhoeals, or a feature of disease progression.

MPS III (subtypes IIIA, B, C and D) is characterised by the deficiency of a specific enzyme involved in catalysing the degradation of glycosaminoglycan (GAG) heparan sulphate, which over time, accumulates in body tissues.¹

Methods

MPS Society's (UK) members

Historically, the MPS Society has held copies of members registration of death certificates which outline the primary terminal event and secondary morbidities of deceased individuals.

Death certificates held on record for the period 1957–2006 were reviewed for possible GI-related causes of death:

- **GI conditions** listed on death certificates **that may have contributed to death** were determined through discussions with medical professionals
- Data on certificates included: age and date at time of death; recorded cause of death

MPS specialist centres in England

Eight centres were contacted to request a retrospective five-year audit (2007–2012) of case notes to identify:

- **GI symptoms** experienced by **living patients**

Centres were requested to note the following GI conditions: diarrhoea, constipation, intolerance to feeds, recto/vaginal fistula, pseudo-obstruction and rectal bleeding.

Data provided included: number of patients (live or deceased) seen at each unit over the five years, age (under or over 18) and gender.

Objectives

- To determine if GI conditions contribute to cause of death in MPS III patients
- To assess the prevalence of GI conditions in patients with MPS III

Results

Death certificates analysis

Mainline demographics

5.1% 7 of 136 death certificates included GI conditions as the possible cause of death

Deaths occurred between 1981 and 2005

18 Mean (±SD) age at death was 18.0 (±9.7) (Table 1)

85.7% (n=6) of seven deaths occurred during the patients' **second decade of life**, i.e. between 11–20 years of age (Figure 1)

Table 1. Patient characteristics of deceased patients with GI conditions listed on death certificates*

| Death certificates (n=7) | |
|--------------------------|-------------|
| Age at death, years | |
| Mean (±SD) | 18.0 (±9.7) |
| Median (range) | 14 (11–39) |
| MPS III subtype | |
| A | 4 |
| B | 2 |
| Unknown | 1 |

*MPS Society data

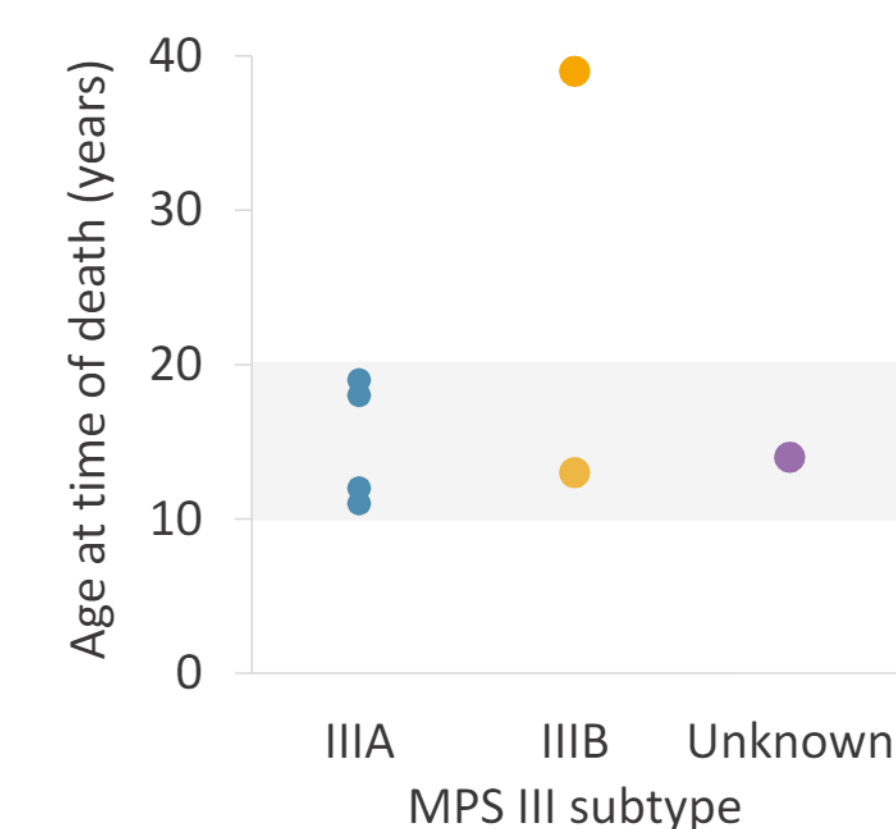


Figure 1. Age of patients at time of death.

GI conditions as a cause of death in MPS III patients

- **Eight GI-related conditions** were listed on the seven death certificates as possible causes of death (Table 2)

Table 2. GI-related conditions listed as a possible cause of death on death certificates of MPS III patients

| Gastrointestinal conditions listed on death certificates* (n=7) | |
|---|---------------------------|
| Abdominal abscess | Haemorrhagic pancreatitis |
| Extreme emaciation (malabsorption) | Paralytic ileus |
| Gastrointestinal bleed | Perforated bowel |
| Gastroenteritis | Peritonitis |

*MPS Society data

[†]A patient could have presented with more than one symptom.

Specialist centre audit (2007–2012)

Mainline demographics

7 specialist centres undertook the audit

80 patients (live and deceased) attended the units over the 5-year period

45% (n=36) of patients were female

74% (n=59) of patients were <18 years of age

GI symptoms/ signs in living patients

- Six specialist centres reported GI conditions in their MPS III patients
- **Four GI conditions** were reported: constipation, diarrhoea, intolerance to feeds and recto/vaginal fistula; there were no patients with pseudo-obstruction or rectal bleeding (Figure 2)
- From the **94 records of GI conditions** reported in current patients, the most frequent were constipation (46.8%) and diarrhoea (45.7%) (Figure 3)

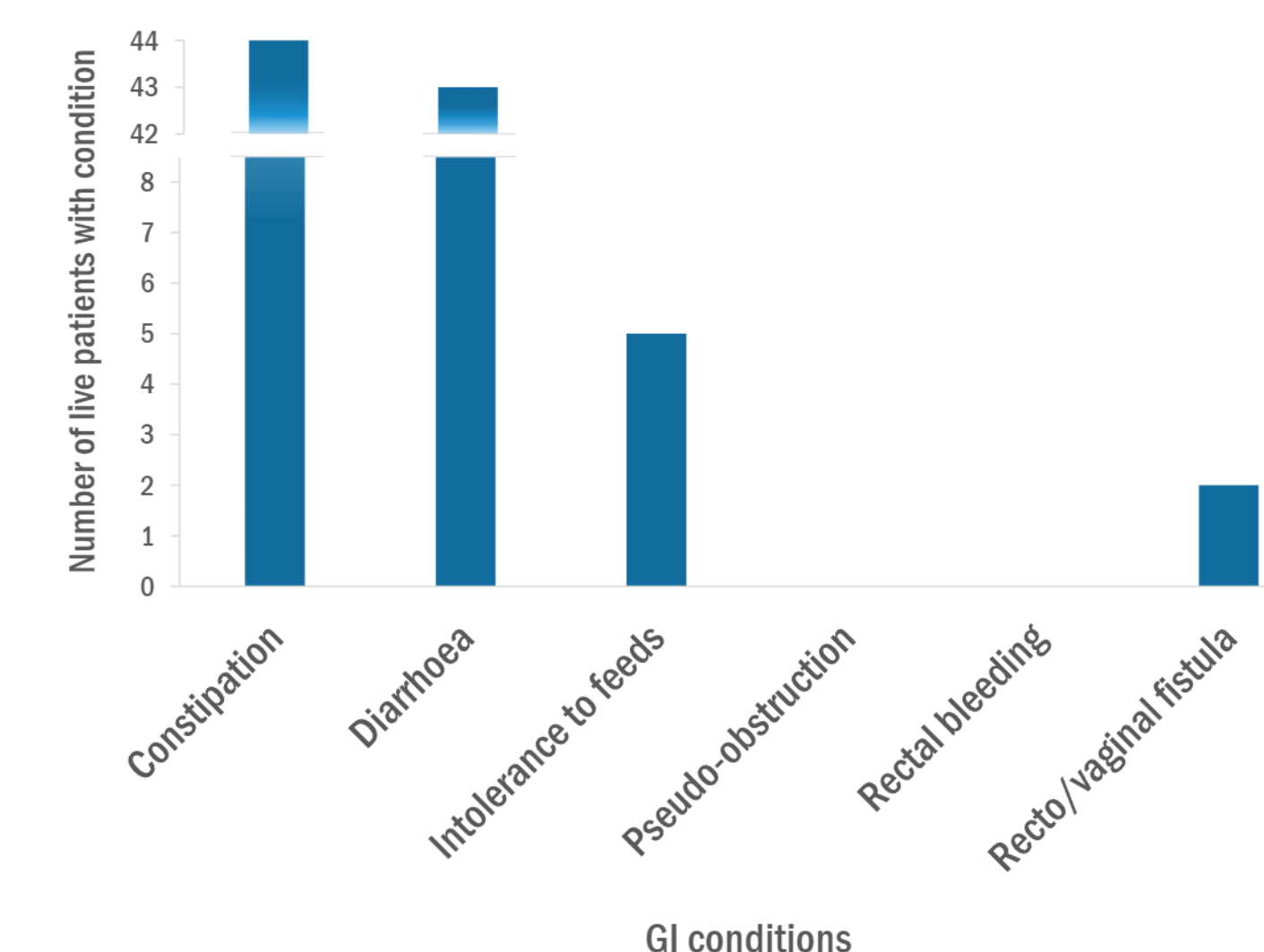


Figure 2. Number of live MPS III patients with GI conditions[†]

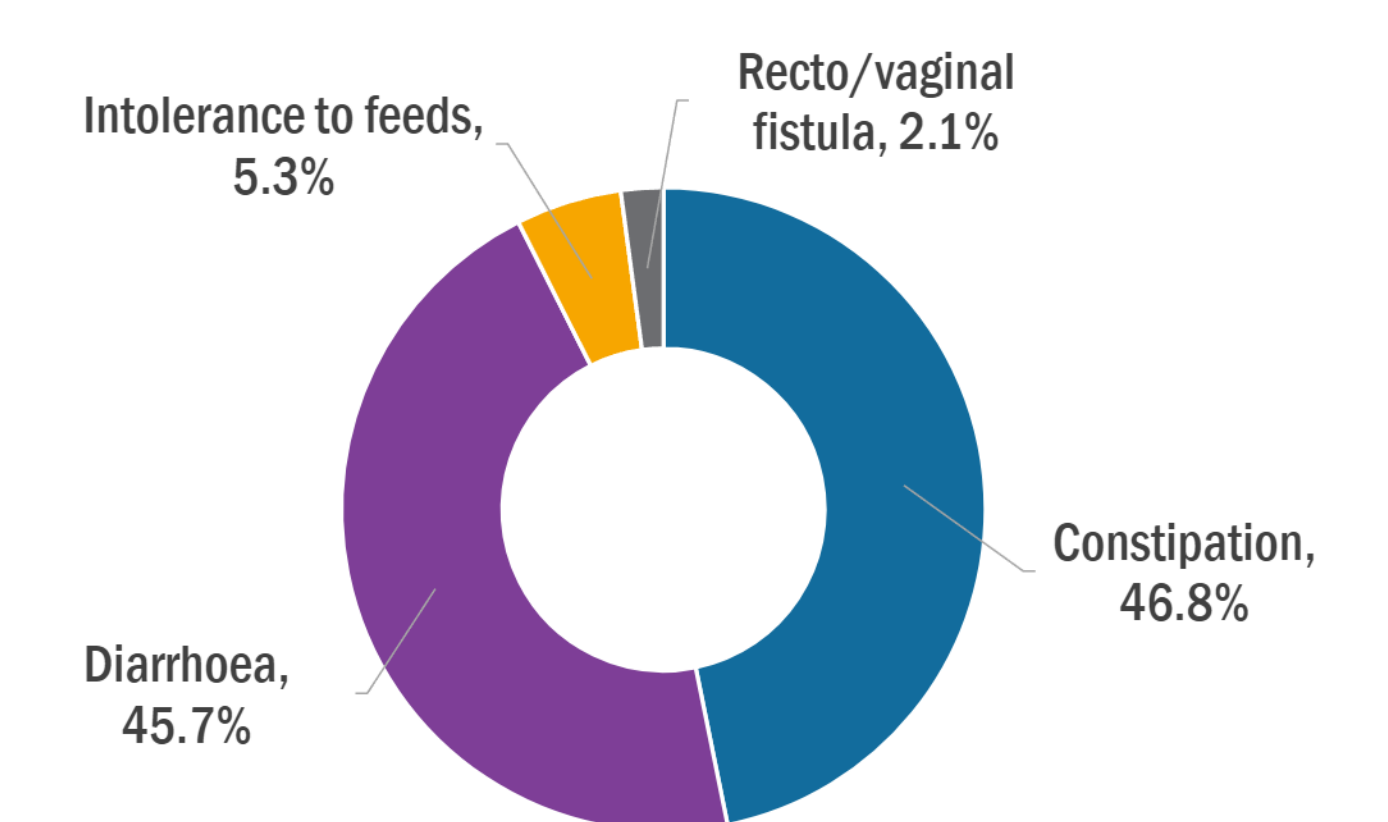


Figure 3. Percentage of each GI condition recorded in live patients in relation to total records (n=94)[†]

References: 1. Valstar MJ, Ruijter JG, van Diggelen OP, Poorthuis BJ, Wijburg FA. Sanfilippo syndrome: a mini-review. J Inher Metab Dis. 2008; 31(2):240–252. 2. Lavery C, Hendriksz CJ, Jones SA. Mortality in patients with Sanfilippo syndrome. Orphanet J Rare Dis. 2017; 12:168–174.

Acknowledgements: The authors would like to thank all specialist clinics for their support with this study; and Dr Jacqueline Adam and Dr Eva Raebel, at Rare Disease Research Partners**, for medical writing support and poster design.

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Key findings

- The **prevalence of GI conditions** as a cause of death was reported in **7 of 136 death certificates (5.1%)** from 1957–2006
- Death certificates listed **8 GI-related conditions** as a possible cause of death
- **Living MPS III patients** at specialist centres had **4 major GI conditions**, with constipation and diarrhoea being the most frequent

Conclusions

Although respiratory infections are the leading cause of death in MPS III patients,² **this retrospective study confirmed that GI conditions can be the primary cause of death in some individuals.**

To be able to support MPS III patients and their families with achieving the best quality of life throughout their disease journey, a prospective study is warranted to ascertain the prevalence, morbidity and mortality associated with GI manifestations in these patients.