Sleep disturbance in Sanfilippo syndrome: a parental questionnaire study

J Fraser, A A Gason, J E Wraith, M B Delatycki

Aims: To determine the incidence, manifestations, and best management of sleep disturbance in Sanfilippo syndrome (mucopolysaccharidosis (MPS) type III).

Methods: Families were ascertained through the MPS societies of Australasia, the UK, and the USA. Questionnaires were sent by mail and were answered anonymously. Identical questions regarding sleep disturbance were asked about unaffected siblings to provide control data. Sleep disturbance was quantified by a total sleep disturbance score.

Results: A total of 141 responses were received; 91.5% of children with Sanfilippo syndrome had sleep disturbance and this was significantly higher than for their unaffected sibs; 77.5% of parents had used medication for this problem, with melatonin and antihistamines being most commonly used. Melatonin and benzodiazepines were reported as the most efficacious. Many different environmental modifications had been employed for this problem and some parents reported success with behavioural therapies.

Conclusions: Sleep disturbance is common, severe, and difficult to manage in Sanfilippo syndrome. Based on the parental responses and its safety profile, melatonin is the first line drug that should be tried. Behavioural therapy should be tried in all with Sanfilippo syndrome and sleep disturbance.

Sanfilippo syndrome or mucopolysaccharidosis type III (MPS III) is an autosomal recessive lysosomal storage disorder that affects about 1 in 20 000 live born children.\(^1\) The affected individual lacks a specific enzyme, resulting in an accumulation of excessive amounts of the glycosaminoglycan heparan sulphate. There are four subtypes of MPS III. The most common is type A, due to a deficiency in heparan N-sulphatase. The other subtypes and causative enzyme deficiencies are types B (alpha-N-acetylglucosaminidase), type C (acetylCoA: alpha-glucosaminide acetyltransferase), and type D (N-acetyl glucosamine 6-sulphatase).

The symptoms of Sanfilippo syndrome result from the accumulation of non-degradable material in the lysosomes of the central nervous system, and somatic manifestations are relatively less severe compared to the other MPSs. Generally, children with Sanfilippo syndrome present with non-specific global development delay, followed by a second period of severe behavioural and sleep disturbance.\(^2\) This second period often begins when the child is 3 or 4 years of age. During the final stage, sleep problems become less of a feature, replaced instead with increasing unsteadiness, swallowing difficulties, and seizures. Life span is markedly reduced.

There are currently no specific treatments for Sanfilippo syndrome. Treatment is therefore aimed at reducing symptomatology and supporting the family. Enzyme replacement therapy is of proven benefit in mild MPS I; however with current technology, it is unlikely to be of benefit in MPS III as the enzyme cannot cross the blood-brain barrier.\(^2\)

Sleep disturbance is a central feature to Sanfilippo syndrome, with 87–92% of patients affected.\(^4\) Reported sleep problems include frequent waking, settling difficulties, and night wandering. We recently surveyed clinicians managing children with Sanfilippo syndrome; in the experience of these clinicians, sleep problems are almost universal.\(^3\) It also revealed that treatment of this problem is very difficult and inconsistent, with melatonin ranked as the single most effective drug.

In this study parents of people affected with MPS III from the USA, UK, and Australia were surveyed to investigate their experiences of sleep disturbance in children with Sanfilippo syndrome and to evaluate what treatments have been successful in dealing with their children’s sleeping problems.

METHODS
Participants
Participants were recruited through the MPS societies of the USA, UK, and Australia. The participants were the parents and carers of individuals with MPS III (including those who had died). Throughout, we have used the term parent to include all primary carers. All responses were anonymous. The study was approved by the Ethics in Human Research Committee of the Royal Children’s Hospital, Melbourne.

Questionnaire details
The questionnaires underwent content validation by a panel of clinicians with expertise in the management of MPSs and an individual with expertise in questionnaire design. This was then piloted on a small group of families with children affected by MPS III. The questionnaire contained general demographic items, Likert scale items on sleep disturbance, details on any medical and behavioural treatments and environmental modifications used, and parental perception of the effectiveness of interventions. Sleep disturbance was assessed by the frequencies of (i) difficulty getting to sleep, (ii) night-time waking, (iii) early morning waking, (iv) daytime sleeping, (v) night-time disruptive, and (vi) dangerous behaviour. A continuous scale for the total prevalence of sleep disturbance (TSD) ranging from never (0 points) to very often (24 points) was determined by the addition of scores from the responses to these six questionnaire items. A subcohort of respondents was surveyed for the same parameters in their children unaffected by MPS III to act as a control group. The complete questionnaire can be found at http://www.genetichealthvic.net.au/pages/Downloads/MPS_survey.doc.

Abbreviations: MPS, mucopolysaccharide; TSD, total sleep disturbance score.

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Statistical procedures

Questionnaire responses were analysed with SPSS for windows (version 11.0, Chicago, IL, USA). Descriptive statistics and univariate procedures were performed for item responses. Parametric comparison of means and analysis of variance tests included both bivariate and multivariate procedures, while non-parametric tests involved two procedures.

RESULTS

General

One hundred and forty one questionnaires were returned (54.6% were from the USA, 32.6% from the UK, and 12.8% from Australasia). Demographic information is shown in table 1. A total of 91.5% of children with MPS III were reported to have sleep problems.

Nature of sleep disturbance

The age of onset of sleep disturbance in individuals with MPS III ranged from birth to 22 years, with ages 3–5 years being the most frequent period in the child’s life when sleep disturbance commenced (fig 1).

The nature of the sleep disturbance was reported through the TSD scale described above and is detailed in table 2. Sleep disturbance was much more frequent in individuals with MPS III than their unaffected siblings (mean TSD 17.3 for those with MPS III, 3.9 for their unaffected sibs, t = 18.31, p < 0.0001). Other parameters such as daytime behavioural problems and seizure activity were also assessed for their association to sleep disturbance. Parents reported there was a relation between behavioural problems during the day and association to sleep disturbance. Parents reported that the treatment of daytime problems and seizure activity were also assessed for their age and onset of sleep disturbance, their TSD score, whether or not they had MPS III affected siblings, or their country of origin (data not shown). Of the parents treating their children with medication, 57.8% (n = 63) had tried only one or two different medications, whereas 11% (n = 12) of parents had tried five or six different drugs.

Parents tried a variety of medications (table 3). Of these, melatonin and antihistamines were the most commonly used. No medication was universally perceived as beneficial. Of the drugs used by more than 30 individuals, melatonin was seen as the most effective, followed by benzodiazepines.

The age of the child was an important factor in the parents’ perception of the benefit of the drug. Melatonin was more likely to help in the treatment of sleep disturbance in younger children (t = −2.04, p = 0.047), while antihistamines were reported to be more effective if the child was younger at the onset of sleep disturbance (t = −2.33, p = 0.024).

Behavioural modification

Thirty seven per cent (n = 52) of parents had used behavioural modification, either alone or in combination with medication. The use of behavioural modification was not statistically associated with the child’s age, age of onset of sleep disturbance, their TSD score, or whether they had MPS III affected siblings (data not shown). However, Australian families were more likely to use behavioural modification techniques (66.7%) than families from the UK (27.9%) or USA (36.7%) (χ² = 18.25, p = 0.006).

The parents’ perceived success of the behavioural modification was either not at all successful (n = 20, 41.7%), moderately successful (n = 21, 43.7%), or very successful (n = 7, 14.6%). Of the 42 families using both medication and behavioural treatments in combination, 50% (n = 21) found the combination more successful than either used in isolation.

Environmental modification

Families reported numerous forms of environmental modification. The commonest reported was the child sleeping

Table 1

<table>
<thead>
<tr>
<th>Number of children (%)</th>
<th>Age range (mean)</th>
<th>Sleep problems</th>
<th>Mean age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0–40 (13.5)</td>
<td>0–43 (13.3)</td>
<td>0–47 (13.8)</td>
</tr>
<tr>
<td>1</td>
<td>129 (91.5)</td>
<td>5 (8.2)</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>2</td>
<td>12 (8.5)</td>
<td>56 (91.8)</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>3</td>
<td>3.8</td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>
with a parent(s). In 22.5% of cases (n = 32), the child slept with their parents every night, while 59.2% of parents (n = 84) never slept with their child. Other forms of environmental modification reported include sleeping harnesses, bed rails and enclosed beds, “stable” doors, television in the child’s room, and closed circuit television.

Parents’ overall view of interventions
Overall, the majority of parents found the treatments they had used for their child’s sleep disturbance to be either acceptable or very acceptable (n = 54, 83%).

DISCUSSION
This study confirms the results of our previous study that sleep problems are significant and prevalent in children with Sanfilippo syndrome. In more than 60% of children these problems had started prior to 5 years of age and therefore predated the diagnosis of MPS III in many.

Families from all three countries had tried a range of medications for this problem. Australian families were more likely to also try behavioural therapy in addition to medication. In agreement with our previous study, melatonin was the single most commonly used drug in all three countries and was rated as helpful in almost 70% of cases. Given these findings and its safety profile, lack of significant side effects, and the fact that tolerance is not observed, this study also leads to the conclusion that melatonin is the first-line agent to use for sleep disturbance in MPS III.

Only 37% of families had tried behavioural modification. In traditional behavioural modification the child is taught more acceptable sleep behaviours by a system of rewards and punishment. This is often successful in children with stable intellectual function; however as Sanfilippo syndrome is marked by progressive deterioration in function, traditional behavioural treatments may become less effective with time. Where not always successful, behavioural therapies have the benefit of being relatively safe and families should be encouraged to try them, either alone or in addition to medication.

A study by Wiggs and Stores investigated behavioural treatments for sleep problems in children with severe learning problems. The majority of children in this study had stable intellectual function. The behavioural interventions were tailored to each child and family, but were based around positive and negative reinforcements and helping the family to elucidate any possible mechanisms maintaining the settling and waking problems. The subjective sleep profiles of the treated children improved when compared to a control group. The sleep patterns of their carers also improved, in fact more so than that of their children.

Environmental modifiers are very important measures used by families to assist with sleep problems. While they don’t solve the problem for the child, they allow parents peace of mind knowing that their child is less likely to come to harm. The environmental modifiers suggested by the families where the child had their own room may prove very beneficial to co-sleeping parents, who often reported a high rate of sleep deprivation from their child’s nocturnal problems.

In our previous study only 36.4% of clinicians reported a link between the child’s sleep and their behaviour. By contrast, in this study, 58% of families reported that there was an association between their child’s sleep problems and their daytime behaviour. This association was usually a negative one, with a poor night’s sleep leading to a sleepy child (68%) and/or a child that was more aggressive/disruptive (51%) and less able to learn and remember (35%). Wiggs and Stores studied 486 children from state special schools. They found that children with sleep problems showed significantly more challenging behaviour than children who slept better.

Sleep apnoea is well described as a cause of sleep disturbance in MPSs. This is much more common in MPS I and II than MPS III. A history of symptoms of sleep apnoea should be sought in all cases of MPS III with sleep disturbance. Because sleep apnoea is rare in MPS III, we do not recommend formal sleep studies in all children with MPS III. In our experience, sleep studies are very difficult to

<table>
<thead>
<tr>
<th>Drug</th>
<th>Individuals using drug; n (%)</th>
<th>Was the drug effective? n (%)</th>
<th>Efficacy of response; n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Good</td>
</tr>
<tr>
<td>Melatonin</td>
<td>58</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>57</td>
<td>49</td>
<td>24</td>
</tr>
<tr>
<td>Choral Hydrate</td>
<td>41</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>38</td>
<td>57</td>
<td>16</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>14</td>
<td>64</td>
<td>5</td>
</tr>
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<td>Antidepressants</td>
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<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Clonidine</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alternative medicine</td>
<td>2</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td>149</td>
<td>106</td>
</tr>
</tbody>
</table>

Table 2: Details of the nature of sleep disturbance for individuals with and without MPS III

Table 3: Frequency of medications used in treatment for sleep disturbance, whether they worked, and the efficacy of response.
conduct because of the behavioural and sleep issues described. However, a history of snoring should be elicited as part of sleep evaluation in all children with MPS III. Children with MPS III who snore should undergo further evaluation to rule out sleep disordered breathing. Until such evaluation is complete, benzodiazepines for sleep disturbance in children with MPS III who snore should be prescribed with caution.

In conclusion:

- Sleep problems are common and severe in MPS III.
- Melatonin appears to be the single most successful sleep inducing agent and the one associated with the fewest side effects. We suggest this be tried as a first line agent. Lack of success of melatonin may be associated with problems such as the child is in pain or the dose is inadequate. The recommended dose is 2–10 mg according to the literature, but higher doses may be needed. Other medications should be introduced if melatonin is unsuccessful. Based on the results of this questionnaire, a benzodiazepine should be the next medication introduced.
- Behavioural therapy should be tried in all children with MPS III and sleep disturbance. Simple strategies such as a bedtime routine, bathing, and darkening the room may help to provide cues to the child that it is time to sleep. Deteriorating intellectual function should not preclude attempting these simple techniques.
- Environmental modification provides the family with some control over their lives and a sense that their child is safe. These measures may also enable carers to have a better quality and quantity of sleep, making their quality of life better and also making them better able to deal with managing a child with this disorder.
- There is a clear need for controlled studies to look at the question of management of sleep disturbance in MPS III in order to formally assess and compare various therapies.

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