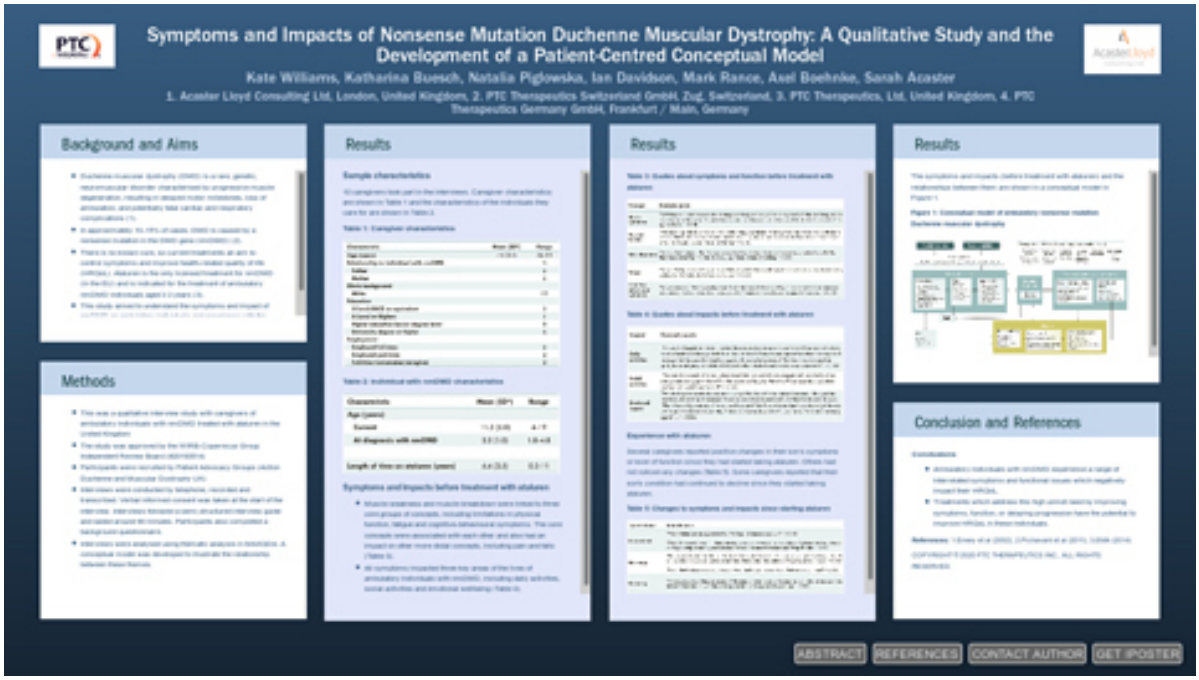
Symptoms and Impacts of Nonsense Mutation Duchenne Muscular Dystrophy: A Qualitative Study and the Development of a Patient-Centred Conceptual Model



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BACKGROUND AND AIMS

- Duchenne muscular dystrophy (DMD) is a rare, genetic, neuromuscular disorder characterised by progressive muscle degeneration, resulting in delayed motor milestones, loss of ambulation, and potentially fatal cardiac and respiratory complications (1).
- In approximately 10–15% of cases, DMD is caused by a nonsense mutation in the DMD gene (nmDMD) (2).
- There is no known cure, so current treatments all aim to control symptoms and improve health-related quality of life (HRQoL). Ataluren is the only licensed treatment for nmDMD (in the EU) and is indicated for the treatment of ambulatory nmDMD individuals aged ≥ 2 years (3).
- This study aimed to understand the symptoms and impact of nmDMD on ambulatory individuals and experience with the drug atatluren

METHODS

- This was a qualitative interview study with caregivers of ambulatory individuals with nmDMD treated with ataluren in the United Kingdom
- The study was approved by the WIRB-Copernicus Group Independent Review Board (#20193514)
- Participants were recruited by Patient Advocacy Groups (Action Duchenne and Muscular Dystrophy UK)
- Interviews were conducted by telephone, recorded and transcribed. Verbal informed consent was taken at the start of the interview. Interviews followed a semi-structured interview guide and lasted around 90 minutes. Participants also completed a background questionnaire.
- Interviews were analysed using thematic analysis in MAXQDA. A conceptual model was developed to illustrate the relationship between these themes.

RESULTS

Sample characteristics

10 caregivers took part in the interviews. Caregiver characteristics are shown in Table 1 and the characteristics of the individuals they care for are shown in Table 2.

Table 1: Caregiver characteristics

Characteristic	Mean (SD*)	Range
Age (years)	44 (5.4)	26-52
Relationship to individual with nmDMD		N
Father		5
Mother		5
Ethnic background		
White		10
Education		
O level/GSCE or equivalent		3
A Level or Highers		1
Higher education below degree level		0
University degree or higher		6
Employment		
Employed full-time		6
Employed part-time		2
Full-time homemaker/caregiver		2

Table 2: Individual with nmDMD characteristics

Characteristic	Mean (SD*)	Range
Age (years)		
Current	11.5 (5.0)	4-19
At diagnosis with nmDMD	3.3 (1.0)	1.8-4.8
Length of time on ataluren (years)	4.4 (3.5)	0.3-11

Symptoms and Impacts before treatment with ataluren

- Muscle weakness and muscle breakdown were linked to three core groups of concepts, including limitations in physical function, fatigue and cognitive-behavioural symptoms. The core concepts were associated with each other and also had an impact on other more distal concepts, including pain and falls (Table 3).
- All symptoms impacted three key areas of the lives of ambulatory individuals with nmDMD, including daily activities, social activities and emotional wellbeing (Table 4).

RESULTS

Table 3: Quotes about symptoms and function before treatment with ataluren

Concept	Example quote
Muscle symptoms	*"Definitely the muscle weakness side of things, not being able to walk for long periods of time, not being able to run and play, suffering with fatigue every day and just physically just not being able to do what other kids of his age could do."* – C108
Physical function	*"We couldn't go places where we had to walk a long way, because he just got so tired. We used to walk him to nursery, which is about I'd say less than quarter of a mile, and he used to have to sit down two or three times on a wall, just to get his breath back, rest his legs"* – C105
Pain/ discomfort	*"He would just complain that his legs were just hurting probably from the knee down, his calves basically, that they would be hurting if he had to do any significant amount of walking."* – C101
Fatigue	*"He would fatigue very quickly, so he wouldn't, he wasn't able to walk very far or climb or run, despite him being cautious but he would also fatigue very quickly"* – C106
Cognitive-behavioural symptoms	*"He was getting a little bit grouchy about the fact that people kept on asking him to concentrate on something, on a piece of work, or even at home doing a bit of homework he would be struggling to focus on it"* – C105

Table 4: Quotes about impacts before treatment with ataluren

Impact	Example quote
Daily activities	*"He would struggle in school…rather than do an hour lesson he would do 20 minutes at a time, have a break and then go back to it. But, he had full one-to-one support at school so they could manage that because he would struggle with some behaviours. If he was tired, he could be quite, he would play up a little bit towards other students and maybe make comments"* – C108
Social activities	*"I've seen it a couple of times, where they'd all rush out into the playground, and he'd just be sitting there up against the wall in the corner, waiting for them to all rush past him, and then he'd sort of waddle out as well"* – C105
Emotional impact	*"We don't go to sports day anymore, we get the day off from school because…they got him involved with helping to manage it and do scoreboards and stuff like that but he was still just, "This is just a big memory of what I can't do and I don't want to be here" and that night he was just in pieces because he was like, "I hate it, I absolutely hate it"…so I said, "He's never coming again"…"* – C104

Experience with ataluren

Several caregivers reported positive changes in their son's symptoms or level of function since they had started taking ataluren. Others had not noticed any changes (Table 5). Some caregivers reported that their son's condition had continued to decline since they started taking ataluren.

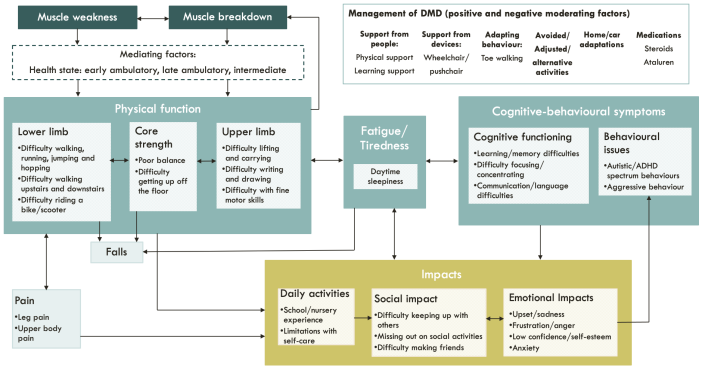
Table 5: Changes to symptoms and impacts since starting ataluren

Type of change	Example quote
Improvement	*"We definitely saw an improvement on the length of time he could walk"* – C108 *"We didn't expect to see him, things like his concentration improving so quickly and actually starting to learn, finding learning an easier process because he's able to concentrate more and things like that"* – C101
No change	*"It's just good to see that [he] can be stable. Obviously we know that things will change at some point but it's a much slower decline so it gives you just more time to play with really and it's just positive all round"* – C108 *"I don't think [ataluren] has any effect on him, I don't think it works, I don't think it has any impact"* – C103
Worsening	*"The drug has slowed the progression of the condition enormously but because of the nature of the condition, he's now worse than he was four years ago or three years ago or two years ago"* – C106

RESULTS

The symptoms and impacts (before treatment with ataluren) and the relationships between them are shown in a conceptual model in Figure 1.

Figure 1: Conceptual model of ambulatory nonsense mutation Duchenne muscular dystrophy



CONCLUSION AND REFERENCES

Conclusions

- Ambulatory individuals with nmDMD experience a range of interrelated symptoms and functional issues which negatively impact their HRQoL.
- Treatments which address this high unmet need by improving symptoms, function, or delaying progression have the potential to improve HRQoL in these individuals.

References: 1.Emery et al (2002), 2.Pichavant et al (2011), 3.EMA (2014)

AUTHOR INFORMATION

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ABSTRACT

Objectives

Duchenne muscular dystrophy (DMD) is a rare genetic neuromuscular disorder which primarily affects boys. It causes progressive muscle degeneration and weakness which leads to loss of motor function and premature death. It is typically diagnosed before the age of five as a result of a delay in reaching motor milestones. Around 10-15% of cases are caused by a nonsense mutation (nmDMD). This study aimed to understand the symptoms of nmDMD and its impact on health-related quality of life (HRQoL).

Methods

Qualitative interviews were conducted with caregivers of individuals with nmDMD treated with ataluren in the UK. An interview guide, developed with input from clinical experts and patient advocacy groups, explored key concepts (symptoms and impacts) associated with nmDMD prior to complete loss of ambulation. Interviews were conducted by telephone, recorded and transcribed. Data were analysed using thematic analysis and saturation was recorded. A conceptual model was developed to illustrate the relationship between symptoms and impacts.

Results

Ten interviews were conducted with the parents of individuals aged 4-19 years. Key symptoms identified were muscle weakness and muscle breakdown, which were associated with limitations in physical functioning (lower limb function, core strength, upper limb function) and pain. Other core concepts included fatigue and cognitive-behavioural symptoms (e.g. learning difficulties and behavioural issues). These symptoms impacted people's daily activities (e.g. limitations with self-care), social activities (e.g. difficulty keeping up with others) and emotional wellbeing (e.g. frustration). These concepts and relationships were illustrated in a conceptual model. Positive and negative moderating factors (e.g. support and treatment) were discussed.

Conclusions

Caregivers reported a range of interrelated symptoms and functional issues which impacted the broader HRQoL of individuals with nmDMD. Treatments which address the high unmet need in this population by improving symptoms, functioning, or delaying progression have the potential to improve HRQoL in these individuals.

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