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SCOPING REVIEW

Interventions in Mowat Wilson Syndrome: A Scoping Review

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Abstract

Mowat-Wilson syndrome (MWS) is a rare autosomal dominant condition caused by a heterozygous mutation or deletion of the ZEB2 gene. The syndrome occurs in both sexes but is potentially more frequently diagnosed in males. The number of new cases is estimated to be 1 in 50,000-70,000 born children. MWS is characterised by a distinctive facial appearance in association with intellectual disability (ID) and a range of other features including epilepsy, and Hirschsprung disease, microcephaly, agenesis of the corpus callosum and congenital heart defects. Epilepsy is considered a main manifestation of the syndrome and affects approximately 80% of individuals with MWS. Developmental milestones are delayed, and speech is limited to a few words. Behavioural and emotional difficulties have also been reported.

This scoping review aimed to identify the existing literature on interventions targeting individuals with MWS and identify gaps in order to guide future research.

A search yielded six studies that encompassed a total of 34 participants, both males and females, with an age span of three months to 45-years-old. The focus of the studies included was medical treatment of epilepsy and surgery for Hirschsprung's disease, with mixed results. One study reported improvement of behavioural problems using psychopharmacological management. Four of the six selected studies had a case-report design. The quality appraisal revealed heterogeneity in the level of details reported and the overall quality of the studies. Hence, the generalisability of the results should be interpreted with caution.

This scoping review shows that studies of interventions targeting symptoms in individuals with MWS are still very scarce. As MWS is a rare disease, it is difficult to conduct randomized controlled trials at a group level. One viable alternative could be single case experimental design studies (SCED) which can reveal experimental effects with just one case. Aggregated findings from such designs can also facilitate recommendations of evidence-based interventions for individuals with rare disorders.

The studies included mainly examined physical health, but other factors also may improve an individual's well-being. Intervention studies in other research areas, for instance, communication, motor functioning, learning, behaviour and participation in daily life activities are therefore called for. It would also be of interest to further examine how functioning in different areas correlates with quality of life for individuals with MWS.

Keywords

Mowat Wilson Syndrome, Intervention, Scoping review

Introduction

Mowat-Wilson syndrome (MWS) is a rare autosomal dominant condition caused by a heterozygous mutation or deletion of the ZEB2 gene [1]. The syndrome occurs in both sexes but is potentially more frequently diagnosed in males (100:70) [1]. The number of new cases is estimated to be 1 in 50,000-70,000 born children, but the prevalence may be underestimated [2]. MWS is characterised by a distinctive facial appearance in association with intellectual disability (ID) and a range of other features including epilepsy, and Hirschsprung disease, microcephaly, agenesis of the corpus callosum and congenital heart defects [3,4].

Epilepsy is considered a main manifestation of the

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syndrome and affects approximately 80% of individuals with MWS [1]. The seizures vary in nature, from absences to generalized seizures and myoclonic seizures [5,6]. Onset of epilepsy usually occurs in the second year of life, but seizures may begin in the neonatal period, in infancy or in late childhood [3,6]. In approximately 25% of cases, the seizures are resistant to treatment [3].

Hirschsprung disease (HSCR), i.e. agenesia of the nerve cells in the colon is commonly reported in individuals with MWS (44%) with various severity [3]. Before the advancement of genetic testing, HSCR was considered the hallmark of MWS. This led to reports of a higher proportion of MWS patients with HSCR and under-diagnosis of patients with MWS but without HSCR [3]. The disease requires early surgery within the first days or months of life, though serious constipation and postoperative faecal incontinence are reported to persist in operated patients [1,7].

Hypotonia is frequent in the first years of life [1]. Developmental milestones such as sitting and walking are delayed, and some individuals remain non-ambulatory. Furthermore, development of fine motor skills is delayed and there is a lifelong need of assistance in their daily care.

Speech is typically limited to a few words, with onset at around 5-6 years. Some patients do not speak at all but may use alternative communication methods, like sign language [8]. Individuals with MWS typically display a happy, sociable demeanour [9].

Clinically significant levels of behavioural and emotional difficulties have also been reported in people with MWS. The levels of behavioural problems were similar in children with MWS compared with age-matched and level of ID-matched controls [9]. Behaviours found to be associated with MWS include repetitive or stereotyped behaviours and oral behaviours such as mouthing and teeth grinding. Evans and collegues [10] found an association between increased behavioural problems and sleep disturbance in individuals with Mowat Wilson syndrome. The finding that the sleep disturbance is related to behavioural disturbance is consistent with previous literature showing an association between sleep problems and increased day time behavioural problems in children [11-13] and adults [14,15] with ID.

Recommendations for multidisciplinary management are currently based on clinical experiences [3]. The health issues associated with the syndrome are complex and sometimes early surgical or pharmacological interventions are needed. Researchers have highlighted that the many symptoms associated with the diagnosis are likely to affect the quality of life of individuals with Mowat Wilson syndrome [4,9,16]. It should therefore be stressed that rehabilitative interventions are also necessary for individuals with Mowat Wilson syndrome [3]. Quality of life (QoL) is increasingly recognised as an important consideration in the care of individuals with disabilities and encompasses objective and subjective components [17,18]. Health-related QoL measures typically assess the degree of symptoms and how they affect daily functioning in different domains [17]. Another approach emphasizes the subjective sense of well-being [18]. Regardless of approach, several factors concerning physical, social and emotional well-being contribute to an individual's quality of life.

Aim

To identify and review the existing literature on interventions targeting individuals with Mowat Wilson syndrome and identify gaps in order to guide future research. More specifically the aim was to examine:

- What are the characteristics of the participants in the studies?
- Which study designs and methods have been used?
- What types of interventions have been performed targeting individuals with Mowat Wilson?
- To what extent are the interventions reported as beneficial or effective?
- What is the scientific quality of the studies included?

Methods

Design

A scoping review is considered appropriate when the aim is to examine the existing literature using a wider and more explorative approach than is the case for systematic reviews. In emerging fields especially, a scoping review may also be relevant to determine areas for further research [19]. Unlike systematic reviews, a priori protocols are typically not registered for scoping reviews, and this was the case for the current study. Mowat Wilson is a relatively new diagnosis, and it was expected that only a smaller number of intervention studies would be identified. Therefore, the wide scope of any potential interventions was chosen. Although quality appraisal is optional in a scoping review, it was included in the current study to provide a fuller view of the existing literature.

Search strategy

To identify studies of interventions targeting individuals of all ages with Mowat Wilson syndrome, searches were conducted in PubMed, PsychINFO, CINAHL and ERIC databases. Literature from all years that were available in the data bases, and all kinds of research designs were reviewed.

The search strategy was a combination of terms for Mowat Wilson syndrome and various terms for

Table 1: Search string in PubMed[1].

Mowat -Wilson syndrome OR Mowat Wilson syndrome OR Mowat Wilson OR Mowat-Wilson
AND
(therapeutics[MeSH Terms]) OR (management) OR (activity, daily living[MeSH Terms]) OR (activity, educational[MeSH Terms]) OR (disease management*[MeSH Terms]) OR (Education[MeSH Subheading]) OR (training) OR (treatment) OR (intervention) OR (therap*)

[1]All search terms that were not MeSH terms were searhed for in "All Fields".

intervention. In addition, searches using a combination of terms for Mowat Wilson syndrome and key terms for specific fields [e.g. physiotherapy OR behaviour management] were conducted. The full search strategy for PubMed is presented in Table 1.

The second step involved examining the reference lists of the studies included to identify any additional relevant literature.

Inclusion and exclusion criteria

Studies based on empirical data that evaluated interventions for individuals with Mowat Wilson syndrome targeting the individual's physical or mental health, abilities or well-being in everyday life were included. Inclusion criteria stated that the articles should be peer-reviewed and in English. Studies including participants with other diagnoses were included if it was possible to isolate the results of the participant(s) with Mowat Wilson syndrome, e.g. single case experimental designs in which each participant's result was presented separately. Studies that only targeted management during surgery were excluded as were studies that did not investigate an outcome in relation to an intervention.

Study selection

The selection process consisted of four stages in accordance with the PRISMA guidelines: a) Identification, b) Screening of title and abstracts, c) Eligibility and d) Inclusion [20]. During the identification phase, searches were conducted as described above in Nov 2021 and resulted in a total of 206 articles. A new search of articles published 2021-2023 was conducted in Feb 2023 which yielded six further publications. As part of the screening process, two of the authors assessed the relevance of the studies by reading titles and abstracts. The authors coded their assessment separately in the online-tool Rayyan (https://www.rayyan.ai/). Disagreements were discussed until consensus was reached. It was agreed that this initial assessment would be more prone to include articles than exclude them so that no relevant articles would be missed. This screening resulted in 18 studies being included. During the eligibility phase, all authors screened the full texts, which resulted in 12 further studies being excluded because they did not meet the inclusion criteria, Figure 1.

Data charting extraction

A data extraction form was adapted from Johnels, et al. [21]. One researcher filled out the form and all authors then reviewed the form (see Table 2). During the review, disagreements were discussed until consensus was reached.

Quality appraisal

The Oxford level of evidence table (CEBM) was used to assess the evidence level of the studies (OCEBM/SIGN Levels of Evidence Working Group). This table covers various research questions regarding interventions such as treatment benefits and prognosis, which was suitable for a review with a broader scope. The Oxford evidence levels were used to assess the evidence level of different intervention study designs. In addition, a quality appraisal regarding the methodology and presentation of the study was conducted. The adapted Evidence-Based Librarianship Critical Appraisal Checklist (EBL-CAC) [22] was used to assess the quality of the studies included. This checklist was chosen due to its relatively broad applicability to different study designs and types. Two authors filled out the form independently. Point-by-point agreement was calculated yielding 85% agreement, thus reaching the mark of 80% which is considered as acceptable agreement [23,24].

Results

After the eligibility process, six articles remained [6,25-29]. Table 2 presents an overview of each article describing the authors, date of publication, country, participants, study design, intervention and reported benefits and effectiveness, including the evidence level and quality appraisal of the study.

Participants

Both males and females, with an age span of three months to 45-years-old were studied. In total, 54 participants with Mowat Wilson syndrome were included.

Study design

The majority of the studies selected had a case-report design (4/6). The study designs of the other studies (2/6) were one retrospective observational cohort study which included 10 participants, and one observational longitudinal cohort study with 40 participants.

Type of interventions and reported benefits

The studies focused on medical treatment and/or vagus nerve stimulation for epilepsy (3/6),

Table 2: Data extraction form.

Author, Year, Country	Participants	Study Design	Intervention	Reported Benefits	Level of Evidence OECBM/SIGN	Quality Appraisal
Benedetti-Isaac, et al. [25] Colombia	1 female, 10-years-old	Case report	VNS stimulation for drug-resistant epilepsy	Reduced seizure frequency at one-year follow-up	-	Poor validity (20%)
Besterman & Hendren [26] USA	1 female, 5-years-old	Case report	Medical treatment for problem behaviours	*Improved sleep *Improved behaviour and learning in school *Decrease in tantrum intensity and frequency	-	Poor validity (40%)
Dagorno, et al. [27] France	10: 5 females, 5 males, aged 2-42 months	Retrospective observational single cohort study	Surgery for Hirschsprung's disease	Surgical complications were common, mixed results at follow-ups	3	Poor validity (42%)
Nosaki, et al. [28] Japan	1 male, 45-years-old	Case report	Medical treatment for drug-resistant epilepsy	Seizure free at nine-month follow-up	-	Valid (75%)
Patel, et al. [29] UK	1 male, three-months-old	Case report, longitudinal	Surgery for Hirschsprung's disease	Normal bowel function at ten-year follow-up	-	Poor validity (20%)
Ricci, et al. [6] Italy	40: 22 females, 18 males, 2-31 years-old	Observational longitudinal cohort study	Medical treatment and VNS for epilepsy	Valproic acid is the most widely used and effective antiepileptic drug in MWS, followed by Levetiracetam	3	Valid (75%)

surgery against Hirschsprung's disease (2/6), and psychopharmacological management of problem behaviours (1/6).

Three of the six studies reported effects of various interventions against epilepsy. A longitudinal cohort study of forty patients documented various types of epilepsy and the various antiepileptic drugs used [6]. Valproic acid was found to be most effective, followed by Levetiracetam but the response to Valproic acid varied from being seizure-free to having no tolerance to the medicine. One patient in this study underwent vagus nerve stimulation (VNS) implantation with little benefit. However, one case report described a young girl with drug resistant multiple bilateral epileptogenic foci who experienced reduced seizure frequency from eight per day to one bi-monthly at 1-year follow-up after VNS stimulation [25]. In another case report by Nosaki, et al. [28] an adult male with drug resistant status epilepticus was reported to be seizure-free at the nine-month follow-up after medical treatment with a multiple anti-seizure drug combination (Levetiracetam, Valproic acid and Zonisamide).

Two of the studies included described effects of interventions against Hirschsprung's disease [27,29]. One of these [27] was a retrospective observational cohort study of pull-through surgery in ten patients (aged 2-42 months, (Mdn = 11) which reported mixed results at follow-ups after 1-17.9 years. Half of the participants had reached good functional outcomes even though they experienced minor post-operative complications. The post-operative course was complicated in the remaining five participants. One case report [29] described surgery of a three-month-old boy with primary Duhamel pull-through resulting in normal bowel function at ten-year follow-up.

One case report [26] described the effects of an intervention targeting behavioural problems such as irritability, aggression and tantrums in a five-year-old girl. A series of different medical regimens (e.g., Ethosuximide, Clobazam, Melatonin, Clonidine and Levetiracetam) showed only marginal effects or even worsened the target behaviours. When administering Dexmethylphenidate to improve the patient's attention span, the problem behaviours increased, new problematic biting behaviour emerged, and ultimately the patient needed a short period of in-patient clinical

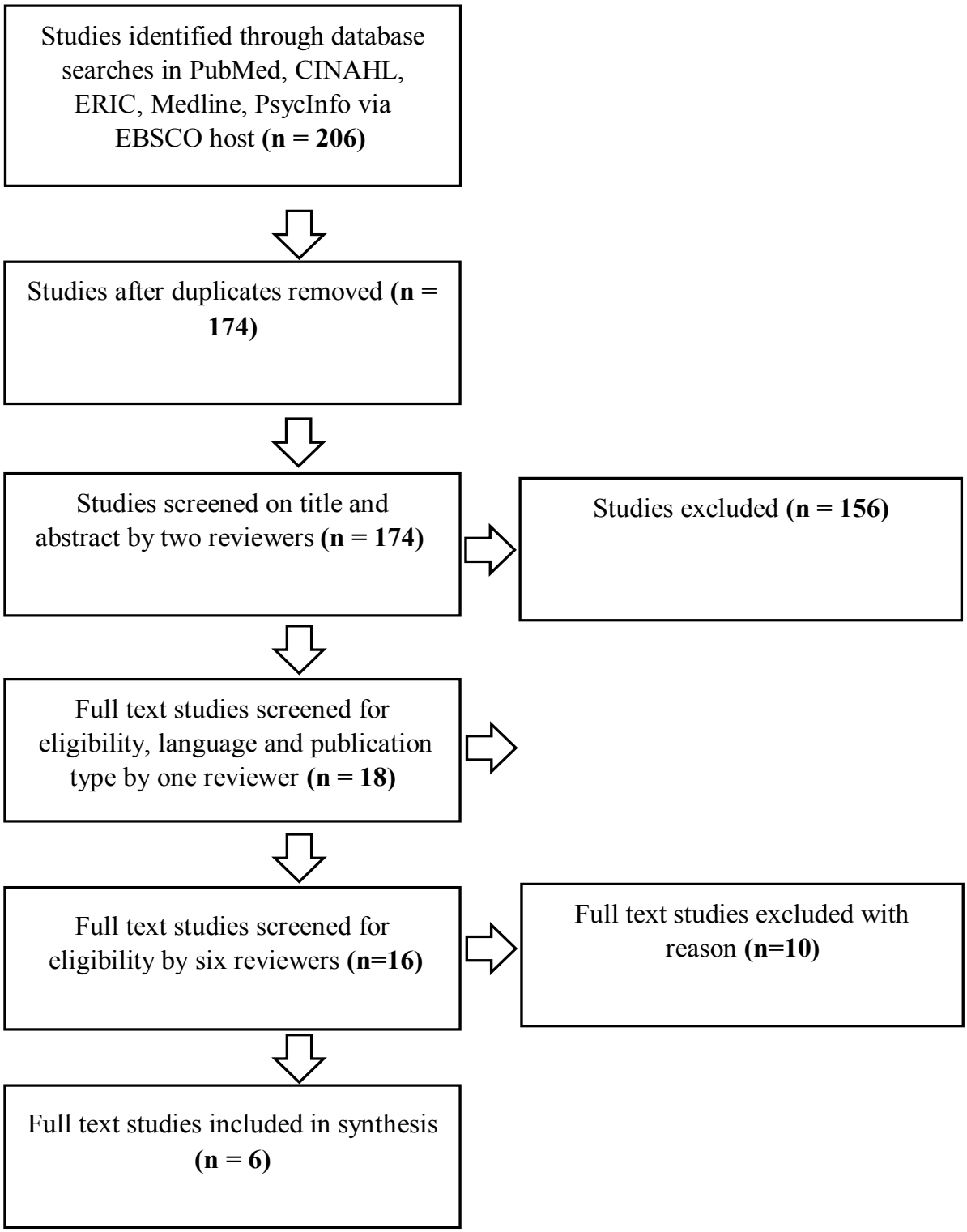

Figure 1: Flowchart of process used to identify and screen studies for inclusion.

treatment. However, when Olanzapine ODT was administered, an immediate decrease in problem behaviours as well as dramatically improved sleep were observed. Furthermore, the patient displayed more adaptive school behaviours and improved learning.

Quality appraisal

The Oxford 2011 level of evidence (CEBM) (OCEBM Levels of Evidence Working Group) and the adapted evidence-based librarianship (EBL-CAC) [22] checklist were used to conduct a critical analysis of the studies included. An overview of the results is provided in Table 2.

In terms of the level of evidence, only two of the studies included were of a study design covered by the typology of the CEBM. These two studies were judged as having level 3 evidence and characterized as being non-randomized, controlled cohort/follow-up studies.

According to the EBL-CAC, the study population

chosen was consistent with the population to which the conclusions were drawn in all studies (6/6). Inclusion and exclusion criteria were not definitively outlined in two of the studies. The alternative "not applicable" was chosen for all case reports (4/6). Only one study had a sample size representative of the entire population. Informed consent from caregivers was reported in four of the studies. Only two studies described data collection methods and the assessment instrument used. All studies measured the outcome of the intervention at an appropriate time (6/6).

In half of the studies (3/6), the methodology seemed to be appropriate. In the remaining studies the information was too limited. In two of the studies, the level of detail was sufficient to allow the study to be replicated. Ethical approval was reported in 50% of the studies. In five of the studies, outcomes were described and discussed in relation to the data collection.

In the majority of the studies (4/6) the conclusions were accurately reflected in the analysis presented. External validity was not obtained in any of the studies. Two of the studies were judged as valid, i.e. had an overall rated validity of ≥ 75%, (Table 2).

Study origin

Of the studies included, one was carried out in Asia, one in North America, one in South America and three in Europe.

Discussion

This is the first review to provide an overview of intervention research in Mowat Wilson syndrome. Mowat Wilson syndrome is characterized by many typical features i.e., symptoms that may consequently affect the QoL of these individuals. The aim of this scoping review was to examine what types of interventions have been performed targeting individuals with Mowat Wilson, and the extent to which the interventions were reported as beneficial. This study also aimed to identify gaps in intervention in order to guide future research. Only six studies which met the inclusion criteria were found, published between the years of 2013 and 2021. As Mowat Wilson is a relatively novel and rare diagnosis, the small number is not surprising.

The quality appraisal revealed heterogeneity in the level of details reported and the overall quality of the studies. The grades varied from poor validity (20%) to high validity (75%), and design types employed represented a lower level of evidence. Only two of the six studies were valid, i.e. had an overall validity of ≥ 75%, and external validity was not obtained in any of the studies. Hence, the generalisability of the results should be interpreted with caution. We nevertheless wish to highlight that this is a young field of research into interventions for this relatively novel diagnosis. Indeed, given the small number of studies within this research area, all studies covered in this scoping review could be seen as pioneering in a way. It is our hope that by scoping the current evidence more research will follow. Four of the six selected studies had a case-report design which is not considered to provide evidence for intervention recommendations. As Mowat Wilson syndrome is a rare disease and only few cases have been identified, it is difficult to conduct randomized controlled trials at a group level.

One viable alternative could be single case experimental design studies (SCED), also called N = 1-studies or N-of-1 trials. High-quality SCED studies can reveal experimental effects with just one case and randomized N = 1 studies have been classified as providing Level 1 evidence for intervention effectiveness and identification of harms [30]. Also, the What Works Clearinghouse (*What Works Clearinghouse procedures and standards handbook, version 5.0. U.S.*, 2022) defines eligibility criteria for a number of SCED variants to qualify for review, and eventually form an evidence base for clinical practices, as in the field of autism [31]. However a review conducted by Müller, et al. [32] revealed that only a few such studies have been used to evaluate interventions in rare genetic neurodevelopmental disorders, and they conclude that the aggregated findings from such designs can also facilitate recommendations of evidence-based interventions for individuals with rare disorders.

The focus of the studies was medical treatment of epilepsy and surgery for Hirschsprung's disease, with mixed results. One study reported improvement of behavioural problems using psychopharmacological management.

The positive effects of Valproic acid in two of the studies [6,28] are consistent with Valproic acid being effective for treatment of various seizure types and particularly for generalized seizures [33,34]. The finding that the effect of different treatments varied between participants, and that combinations of drugs were reported, is not surprising as drug-resistant epilepsy is common in Mowat Wilson syndrome [3,5]. For one patient, Vagus nerve stimulation (VNS) to treat epilepsy was effective at the one-year follow-up while for another patient no effects could be seen. It is not possible nor within the scope of this review to establish the source of this discrepancy between the results. The effect of VNS also differs in a broader population. In a recent study, Kostov, et al. [35] examined long-term outcomes reported in all (N = 436) patients from a VNS quality registry. At follow-up, 58% of the participants responded well to the treatment while 42% were classified as non-responders. Intellectual disability was associated with less favourable outcomes, a finding that supports earlier research [36]. The reason for this is not fully understood. An interesting avenue to pursue further is the correlation between enhanced intrinsic

connectivity within thalamocortical circuitry and seizure response following VNS, which was reported by Ibrahim, et al. [37].

The effects of surgery against Hirschsprung's disease show mixed results, which is in line with the outcomes in wider populations. Townley, et al. [38] examined effects including quality of life measurements 0.7-13.3 years after pull-through surgery in 56 participants with Hirschsprung's disease. PedsQL, a parent-reported assessment of health-related quality of life in children, was used. The tool consists of four scales: physical functioning, emotional functioning, social functioning and school functioning. The correlation between bowel function and quality of life was moderate, and across the whole study group there was no difference between the participants and health controls. Other factors thus impact quality of life. Nevertheless, persisting symptoms may impact several domains of every-day life [39].

This scoping review shows that studies of intervention targeting symptoms in individuals with Mowat Wilson syndrome are still very scarce. Thus far, the intervention studies mainly examined physical health, which does indeed most likely affect an individual's quality of life. We would like to emphasize, however, that other factors also improve an individual's well-being. To improve the quality of life of individuals with Mowat Wilson, intervention studies in other research areas, for instance, communication, motor functioning, learning, behaviour and participation in daily life activities are called for. Considering the study by Townley, et al. [38] it would be of interest to further examine how functioning in different areas correlates with quality of life for individuals with Mowat Wilson syndrome.

Disclosure

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Author Contributions

All authors participated in planning the review. MDM and HW performed the search and abstract review, all authors participated in the full text review. All authors participated in preparation of the manuscript.

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