Scoping Review of Symptoms in Children with Rare, Progressive, Life-Threatening Disorders

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ABSTRACT

Background: Q3 conditions are progressive, metabolic, neurological, or chromosomal childhood conditions without a cure. Children with these conditions face an unknown lifespan as well as unstable and uncomfortable symptoms. Clinicians and other health care professionals are challenged by a lack of evidence for symptom management for these conditions.

Aims: In this scoping review we systematically identified and mapped the existing literature on symptom management for children with Q3 conditions. We focussed on the most common and distressing symptoms, namely alertness, behavioral problems, bowel incontinence, breathing difficulties, constipation, feeding difficulties, sleep disturbance, temperature regulation, tone and motor problems and urinary incontinence. For children with complex health conditions, good symptom management is pertinent to ensure the highest possible quality of life.

Methods: Scoping Review. Electronic database searches in Ovid MEDLINE, Embase and CINAHL and a comprehensive grey literature search.

Results: We included 292 studies in our final synthesis. The most commonly reported conditions in the studies were Rett syndrome (n=69), followed by De Lange syndrome (n=25) and tuberous sclerosis (n=16). Tone and motor problems was the most commonly investigated symptom (n=141), followed by behavioral problems (n=82) and sleep disturbance (n=71).

Conclusion: The evidence for symptom management in Q3 conditions is concentrated around a few conditions and these studies may not be applicable to other conditions. The evidence is dispersed in the literature and difficult to access, which further challenges health care providers. More research needs to be done in these conditions to provide high quality evidence for the care of these children.

Running head: Scoping Review to Examine Symptoms

BACKGROUND

Quadrant 3 (Q3) conditions are progressive, metabolic, neurological, or chromosomal childhood conditions for which there currently exists no curative treatment. They are also known as Category 3 conditions in the report by the UK-based charity, Together for Short Lives.[1] Children with these conditions face an unknown lifespan and symptoms that are both unstable and uncomfortable. Although the individual diagnoses are rare, Q3 conditions are a significant cause of disability and death in childhood. These conditions are numerous and varied, however, collectively they share many features in symptoms and burden of care. Children with Q3 conditions are living longer due to medical advances, but extending the duration of life does not necessarily mean improving a child's quality of life. Until cures are found, a clinician's obligation is to maximize comfort and quality of life. There is a lack of research on these conditions and, particularly, their associated symptoms. Clinicians, health professionals and families caring for children with Q3 conditions are challenged by this lack of research, which limits their ability to make evidence-based care decisions. Our aim in this scoping review was to systematically identify and map the literature regarding the assessment and management of the most common symptoms in Q3 conditions. With better evidence, clinicians and families will be able to make informed decisions about care and ensure better health outcomes for children living with distressing symptoms of complex conditions.

METHODS

Search Methods

Our comprehensive search strategy combined 181 Q3 conditions and 10 symptoms. Q3 conditions were identified through an initial pilot literature search, our previous work in this

area[2,3] and 2 lists of Q3 conditions written by experts in the field.[4,5] When creating the search strategy for the Q3 conditions we were challenged by the lack of controlled vocabulary for many of these conditions in the databases we searched. To ensure complete retrieval of all relevant studies we included broader controlled vocabulary terms when a specific condition term was not available or had only been recently added to the database. For example, "Farber Lipogranulomatosis" was introduced as a MeSH term in 2009, so to ensure coverage to database inception we also included the broader MeSH terms "Lipidoses" and "Sphingolipidoses" that had been previously used to index this condition. See Supplementary File 1 for our full MEDLINE Search Strategy.

The 10 symptoms identified in our pilot study were based on Hunt,[6] Malcolm et al.[7] and our Charting the Territory study.[8] The investigated symptoms were *alertness* (fatigue, arousal, wakefulness, concentration); *behavioral* (agitation, irritability, aggression, self-harm, negative affect); *bowel incontinence*; *breathing difficulties* (dyspnea, cough, apnea, hypoventilation, obstruction); *constipation*; *feeding difficulties* (gastric reflux, regurgitation, emesis, retching, nausea, feeding intolerance, salivary secretions, dyspepsia, swallowing difficulty, aspiration); *sleep disturbance*; *temperature regulation*; *tone and motor problems* (spasticity, dystonia, ataxia); and *urinary incontinence*. Seizures and pain were excluded from the symptom list as seizures is a common symptom with extensive literature and pain is the subject of another scoping review by one of our investigators. "Symptom management" search terms based on the clinical experience of the investigators were added to increase the specificity of the search.

We searched MEDLINE (Ovid), Embase and CINAHL from inception until January 2018; we did not limit our search by publication date or by language. To locate grey literature sources we searched ClinicalTrials.gov, WHO International Clinical Trials Platform, Conference

Proceedings Citation Index- Science (Web of Science), TRIP, ProQuest Dissertations and Theses Global, OAIster and LILACS. Experts in the field were contacted through relevant listservs to locate unpublished studies. Palliative care conferences were identified and conference abstracts were hand-searched when not indexed in the electronic databases already searched. The references of all included studies were hand-searched and Web of Science was used to search the citing articles of each study.

Study Inclusion

Studies had to 1) include at least one of the 181 Q3 conditions, 2) report on at least one of the 10 symptoms and 3) be focused on assessment tools to evaluate symptoms or on interventions to relieve symptoms. We only included studies with pediatric populations (0-18 years) or studies with adults were there was more than one pediatric participant. We excluded non-studies (i.e. letters to the editor, commentaries) and case reports with a single participant. Languages other than English or French were excluded due to a lack of resources for translation.

Study Selection

All search results were imported into Endnote© and duplicates were removed. Due to the comprehensiveness of our search strategy, we returned a large number of results. To more efficiently filter these results, a single team member pre-screened by title and abstract to remove articles that did not include both a symptom and a Q3 condition. The titles and abstracts of the remaining articles were screened in more depth independently and in duplicate by team members using abstrackr.[9] The resulting full-text of studies were then reviewed by team members independently and in duplicate using Rayyan.[10] For articles where the 2 team members did not agree in both the screening and review phases, the team met to come to a consensus decision to

include or exclude. Data were extracted from the remaining full text articles using a database created in REDCap.[11] We extracted data on study design, sample size, tools or scales, intervention, year of publication, journal, Q3 condition(s), symptom(s), study objective, and primary outcome(s). To summarize the charted data, we grouped the studies together by symptom and summarized the study design and study objective. We did not register the protocol for our review our scoping review. We used the PRISMA Extension for Scoping Reviews guidelines to report the methods of our scoping review.[12]

RESULTS

Our database and grey literature search retrieved 46,644 results. We returned a high number of results due to the broadness of our search and the lack of controlled vocabulary for these conditions. Once duplicates were removed, we pre-screened 36,447 and excluded 35,294 for not including both a Q3 condition and a symptom from our list. For this phase, when there was ambiguity the team member always chose to include studies for the next phase. The resulting 1,153 titles and abstracts were then screened and 316 were excluded for lack of symptom focus, wrong study design or wrong population. The remaining 837 full-text articles were reviewed and 545 were excluded for lack of symptom focus (n=206), lack of assessment (n=73), publication type (reviews, letters, commentaries: n=68), ongoing studies without finalized data (n=57), wrong outcome (n=46), wrong population (n=39), not in English or French (n=24), wrong study design (n=14), background article (n=17), and full-text not available (n=1). This left 292 studies in our final synthesis. See Figure 1 for the PRISMA Flowchart of the study selection process.

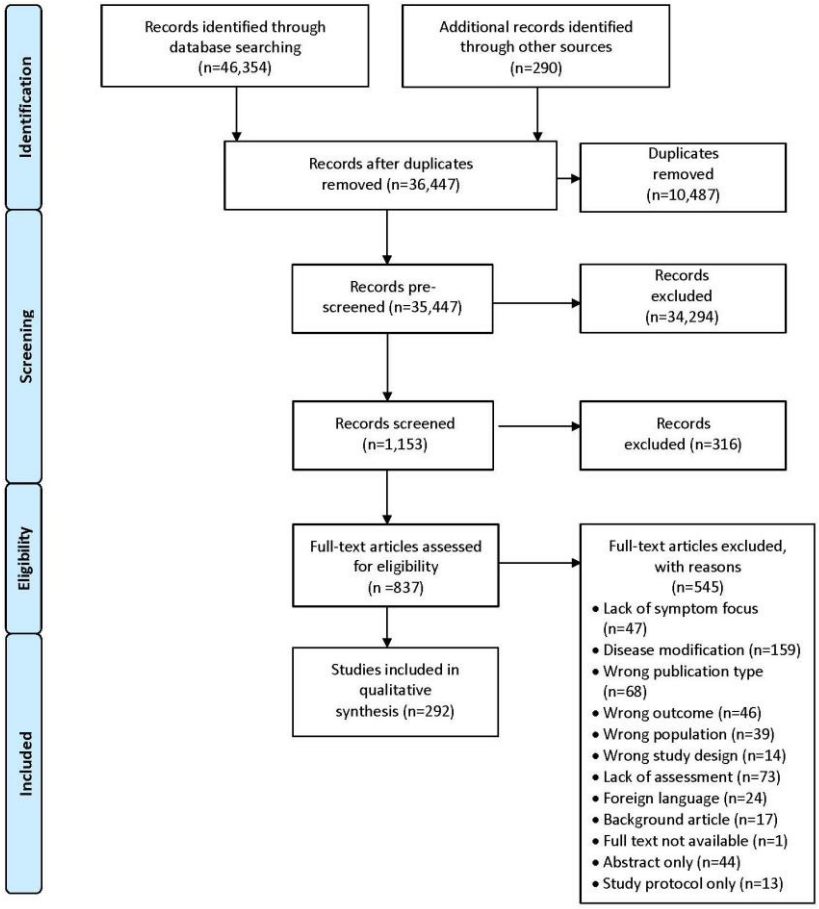


Figure 1: PRISMA flow chart of study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Characteristics

One of the studies was a thesis and the other 291 studies were journal articles. The 291 studies were published in 112 different journals and 70 of these journals only had a single study to contribute to this review. See Table 1 for the 10 most common journals. There was only 1 general pediatric journal, the *Journal of Pediatrics*, that had 3 studies to contribute to this review. The other journals are from a wide variety of disciplines, including clinical neurology, surgery, education, rehabilitation, dermatology, genetics, otorhinolaryngology, palliative care and gastroenterology. The studies were published between 1974 and 2018, with 52% (152) published

in 2010 or later. Fifty-nine percent of the studies used only validated tools or scales, while 27% used non-validated tools or scales, and 14% combined both validated and non-validated tools. See Supplementary File 2 for a table of the characteristics and a full bibliography of all included studies.

Table 1: 10 most common journals

Journal Name	**Frequency of Articles**	**2017 Journal Impact Factor**
Developmental Medicine & Child Neurology	20	3.289
Journal of Intellectual Disability Research	16	2.026
Journal of Child Neurology	13	1.665
American Journal of Medical Genetics Part A	12	2.264
Movement Disorders	11	8.324
Pediatric Neurology	11	2.398
Brain & Development	9	1.544
European Journal of Paediatric Neurology	9	2.362
Journal of Neurodevelopmental Disorders	8	3.500
International Journal of Pediatric Otorhinolaryngology	7	1.305

Q3 Conditions

Rett syndrome was the most investigated Q3 condition (n=69) followed by De Lange syndrome (n=25), tuberous sclerosis (n=16), mucopolysaccharidosis type III (n=15), spinal muscular atrophy type 1 (n=15), Cri-du-Chat (n=14), Friedrich's ataxia (n=13), neuronal ceroid lipofuscinosis type 3 (n=13), and Lesch-Nyhan syndrome (n=12). Only 20 conditions comprised

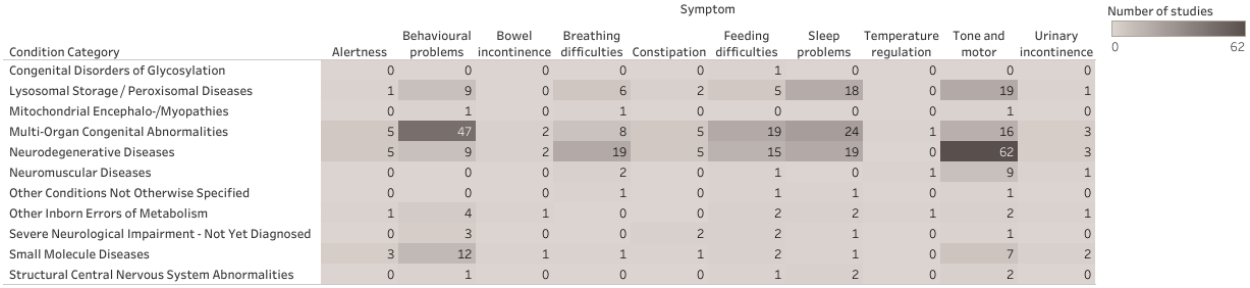
80% of the studies (Table 2). One hundred and twenty-four of the 181 Q3 conditions did not appear in a single study and the remaining 36 conditions were investigated in 5 or fewer studies. See Supplementary File 1 for a heat map of all Q3 conditions and symptoms.

Table 2: 20 most common Q3 Conditions

Q3 Condition	**Frequency of studies**	**Q3 Condition**	**Frequency of studies**
Rett syndrome	69	Epidermolysis bullosa	10
De Lange syndrome	25	Infantile neuroaxonal dystrophy	10
Tuberous sclerosis	16	Mucopolysaccharidosis type I	10
Mucopolysaccharidosis type III	15	Mucopolysaccharidosis type II	10
Spinal muscular atrophy 1	15	Achondroplasia	8
Cri-du-chat	14	Ataxia telangectasia	8
Friedrich's ataxia	13	Mucopolysaccharidosis VI	8
Neuronal ceroid lipofuscinosis 3	13	Glutaric acidemia type I	6
Lesch-Nyhan syndrome	12	Mucopolysaccharidosis type IIIA	6
Jacobsen syndrome	10	West syndrome	6

Using a classification system for these conditions,[3] Neurodegenerative Diseases was the most investigated condition category (n=102), followed by Multi-Organ Congenital Abnormalities (n=97), Lysosomal Storage / Peroxisomal Diseases (n=45), Small Molecule Diseases (n=20), Neuromuscular Diseases (n=14), Other Inborn Errors of Metabolism (n=8), Severe Neurological Impairment -Not Yet Diagnosed (n=7), Structural Central Nervous System Abnormalities (n=5), Other Conditions Not Otherwise Specified (n=4), Mitochondrial Encephalo-/Myopathies (n=2),

and Congenital Disorders of Glycosylation (n=1). See Figure 2 for a heat map of condition categories and symptoms.



Condition Category	Alertness	Behavioural problems	Bowel incontinence	Breathing difficulties	Constipation	Feeding difficulties	Sleep problems	Temperature regulation	Tone and motor	Urinary incontinence
Congenital Disorders of Glycosylation	0	0	0	0	0	1	0	0	0	0
Lysosomal Storage / Peroxisomal Diseases	1	9	0	6	2	5	18	0	19	1
Mitochondrial Encephalo-/Myopathies	0	1	0	1	0	0	0	0	1	0
Multi-Organ Congenital Abnormalities	5	47	2	8	5	19	24	1	16	3
Neurodegenerative Diseases	5	9	2	19	5	15	19	0	62	3
Neuromuscular Diseases	0	0	0	2	0	1	0	1	9	1
Other Conditions Not Otherwise Specified	0	0	0	1	0	1	1	0	1	0
Other Inborn Errors of Metabolism	1	4	1	0	0	2	2	1	2	1
Severe Neurological Impairment - Not Yet Diagnosed	0	3	0	0	2	2	1	0	1	0
Small Molecule Diseases	3	12	1	1	1	2	1	0	7	2
Structural Central Nervous System Abnormalities	0	1	0	0	0	1	2	0	2	0

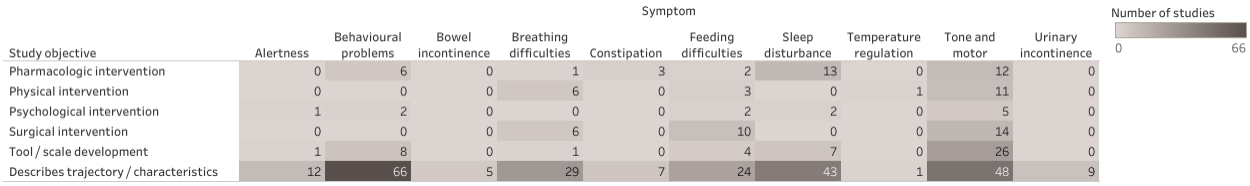
Figure 2: Heat map of Q3 condition categories and symptoms

Symptoms

Alertness

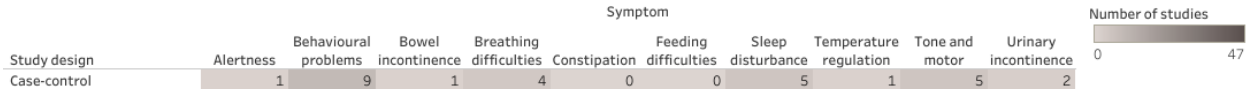
Fourteen studies investigated alertness in Q3 conditions: 11 cross-sectional, 1 case-control, 1 open label and 1 tool/scale development study. The single open-label study investigated a psychological intervention in Rett syndrome: structured training to increase attention and reduce help needed.[13] Paulsen et al. conducted an initial validation of the PedQL Fatigue Scales in Friedrich's ataxia.[14] The remaining 12 studies provided evidence of the severity of this symptom and described its trajectory. See Figure 3 for a heat map of the study objectives and symptoms and Figure 4 for a heat map of symptoms and study designs. For children who have attentional difficulties, clinical practitioners could try structured training, as this was found to be effective in one study in Rett syndrome. Rett syndrome has a distinct clinical profile, so structured training may not be effective in other Q3 conditions. No effective interventions were found for fatigue or alertness. Future studies should focus on other Q3 conditions that may be more applicable to the

group as a whole. A single study suggests the PedQL Fatigue Scales may be useful to measure levels of fatigue in Friedrich's ataxia, which may be useful in other Q3 conditions.



Study objective	Alertness	Behavioural problems	Bowel incontinence	Breathing difficulties	Constipation	Feeding difficulties	Sleep disturbance	Temperature regulation	Tone and motor	Urinary incontinence
Pharmacologic intervention	0	6	0	1	3	2	13	0	12	0
Physical intervention	0	0	0	6	0	3	0	1	11	0
Psychological intervention	1	2	0	0	0	2	2	0	5	0
Surgical intervention	0	0	0	6	0	10	0	0	14	0
Tool / scale development	1	8	0	1	0	4	7	0	26	0
Describes trajectory / characteristics	12	66	5	29	7	24	43	1	48	9

Figure 3: Heat map of study objectives and symptoms



Study design	Alertness	Behavioural problems	Bowel incontinence	Breathing difficulties	Constipation	Feeding difficulties	Sleep disturbance	Temperature regulation	Tone and motor	Urinary incontinence
Case-control	1	9	1	4	0	0	5	1	5	2
Case-series	0	9	0	7	1	11	5	1	27	0
Cohort study	0	0	0	0	0	0	0	0	3	0
Cross-sectional	11	47	4	13	5	15	38	0	26	6
Logitudinal	0	5	0	4	0	2	5	0	15	0
N of 1 trial	0	1	0	0	0	0	0	0	3	0
Open-label	1	2	0	0	1	2	3	0	7	0
Randomized controlled	0	1	0	2	0	0	8	0	2	0
Retrospective chart review	0	2	0	5	3	12	1	0	11	0
Survey	0	9	0	4	2	3	6	0	5	1
Systematic review	0	3	0	2	0	0	1	0	3	0
Tool/ scale development	0	9	0	1	0	3	6	0	26	0

Figure 4: Heat map of study designs and symptoms.

Behavioral Problems

The majority of the 82 studies investigating behavioral problems were cross-sectional (n=47), followed by case control (n=9), case series (n=9), tool or scale development (n=9), survey (n=9), longitudinal (n=5), open-label (n=2), retrospective chart review (n=2), N of 1 trial (n=1) and RCT (n=1). Eight studies investigated an intervention: 6 were pharmacologic and 2 were psychological. Six of the studies were in Lesch-Nyhan syndrome and investigated strategies to reduce or eliminate self-injurious behavior.[15–20] Nyhan et al. tested 5-hydroxytryptophan in a case-series;[15] Khasnavis et al. tested Ecopipam in a RCT;[16] Anderson et al. tested L-5-hydroxytryptophan in a case-series;[17] Mizuno compared L-5-Hydroxytryptophan, L-tryptophan

or levodopa in a case-series;[18] and Visser et al. investigated levodopa and carbidopa.[19] Anderson et al. also investigated if electric shock, positive reinforcement, or time-out reduced self-injury.[20,21] In a case-control study Sloneem et al. investigated how environmental conditions (demand, denial, attention, no contact) affected self-injurious behavior in De Lange syndrome.[22] Ucar et al. investigated risperidone in children with mucopolysaccharidosis type III in an open-label trial.[23]

Eight studies designed and/or aimed to validate scales or tools. Darling et al. designed and pilot tested a disease rating scale for pantothenate kinase-associated neurodegeneration that included a section on psychiatric symptoms.[24] In 2 studies, de Vries et al. and Lezlezio et al. designed and pilot-validated the TAND Checklist for tuberous sclerosis, which includes questions on behavioral concerns.[25,26] Mount et al. developed the Rett Syndrome Behaviour Questionnaire.[27] In 3 studies, Rojahn et al. developed and validated the Behavior Problems Inventory in unspecified intellectual disabilities.[28–30] Shapiro et al validated the Sanfilippo Behavior Rating Scale in mucopolysaccharidosis type III.[31] The remaining 66 studies provided insight into the behavioral challenges faced by caregivers of children with Q3 conditions, identified the possible mechanisms of self-injury, or described the trajectory of this symptom.

Behavioural problems was the second most studied symptom, and most of the studies that investigated interventions focused on self-injurious behaviour. None of the pharmacologic studies showed clear and lasting effects on self-injury. Clinicians could suggest positive reinforcement and/or time-outs, as this led to reductions in self-injury in one study, while punishment led to increased self-injury. Three systematic reviews and 1 RCT were found for behavioral problems, which highlights the need for more high level studies to be conducted on

this challenging symptom. Some condition-specific scales have been created and/or validated for behavioral problems and may be valuable for other Q3 conditions as well.

Bowel Incontinence

Five studies investigated bowel incontinence: 4 cross-sectional and 1 case-control. All the studies described incidence and/or trajectory. Bowel incontinence was the second least studied symptom. Although studies included in this review found that this is a common symptom in Q3 conditions, no studies provide evidence on which to base symptom management.

Breathing Difficulties

Thirty-seven studies investigated breathing difficulties: 13 cross-sectional, 7 case-series, 5 retrospective chart reviews, 4 case-controls, 4 longitudinal, 4 surveys, 2 systematic reviews, 2 RCTs and 1 tool/scale development. Seven of the studies investigated an intervention; six of these examined a combination of surgical and physical interventions. Only 1 study investigated a pharmacologic intervention: testing the efficacy of oral naltrexone in children with Leigh syndrome and other children with sleep apnea in an RCT.[32] In a retrospective chart review, Tenconi et al. assessed conventional treatment options (adenotonsillectomy, continuous positive airway pressure (CPAP), losing weight) for obstructive sleep apnea (OSA) in children with achondroplasia.[33] Also in achondroplasia, a case-series investigated surgery, CPAP, bilevel positive airway pressure, cervical decompression for OSA.[34] In a RCT, Sudarsan et al. compared adenotonsillectomy and CPAP in children with mucopolysaccharidosis types I, II, III, VI and VII.[35] Another retrospective chart review of children with mucolipidosis types II and III and mucopolysaccharidosis types I, II and III, recorded interventions used for respiratory complications, including surgery (adenotonsillectomy, tracheostomy); low flow oxygen;

medications (diuretics, theophylline, digoxin, beta adrenergic blockers, calcium antagonists).[36] Nabatame et al. and Mellies et al. investigated the efficacy of non-invasive positive pressure ventilation for sleep disordered breathing in glycogen storage disease type II and spinal muscular atrophy type 1 respectively.[37,38] Mount et al. developed the Rett Syndrome Behavior Questionnaire that includes questions on breathing problems including air swallowing, breath holding and hyperventilation.[27] The remaining 29 studies described breathing difficulties in this population and provided insight into its trajectory.

Many of the studies confirm the prevalence of both sleep apnea and other breathing problems in Q3 conditions. Sleep apnea studies in achondroplasia suggest surgical intervention may be necessary, while for other Q3 conditions CPAP appears to be effective. Medications, such as naltrexone, could also be effective for sleep apnea. For other breathing problems, 1 study suggested a combination of surgical and pharmacological interventions may be effective, but a systematic review on treatments for dyspnea found the evidence to be of low quality. Our review also shows that overall there is a lack of high level evidence breathing difficulties and more research is needed. One of the studies created a Rett syndrome specific tool that includes a section on breathing problems, which may not be relevant to other Q3 conditions.

Constipation

Ten studies investigated constipation: 5 cross-sectional, 3 retrospective chart reviews, 2 surveys, 1 case-series and 1 open-label study. Three of the studies tested a pharmacological or dietary intervention to reduce constipation. In retrospective chart review, Mordekar et al. investigated parenteral nutrition in Rett syndrome, mucopolysaccharidosis type III and West syndrome[39] and Murata et al. investigated supplementary carnitine in neuronal ceroid lipofuscinosis type 3,

Pelizaeus-Merzbacher disease, tuberous sclerosis and West syndrome.[40] In an open-label study Haynes et al. investigated fiber-containing formula in epidermolysis bullosa.[41] No studies developed or validated a tool or scale and the remaining 7 studies described the features or trajectory of this symptom.[41] To help manage constipation in Q3 conditions, clinical practitioners can try parenteral nutrition, fiber-enriched formula, or supplementation with carnitine. In our Charting the Territory study we found constipation to be the fourth most commonly reported symptom by caregivers, yet only 3 studies investigate symptom management in this population.[8] More studies are needed for this symptom.

Feeding Difficulties

Forty-five studies investigated feeding difficulties: 15 cross sectional, 12 retrospective chart reviews, 11 case series, 3 scale/tool development, 3 surveys, 2 longitudinal and 2 open-label. Thirteen studies investigated an intervention and 10 of these were surgical interventions. Seven of the surgical studies investigated balloon dilation of esophageal strictures in epidermolysis bullosa.[42–48] Stehr et al. and Seguy et al. performed retrospective chart reviews of percutaneous gastrostomy placement in epidermolysis bullosa,[49] spinal muscular atrophy type 1 and other congenital muscular dystrophies and congenital myopathies.[50] Blommaert et al. reported a case series of bilateral submandibular gland excision and parotid duct ligation for drooling in children with MEGDEL syndrome.[51] Two of the studies investigated a pharmacological intervention. Kawai et al. performed an open-label study of baclofen for emesis and gastroesophageal reflux disease in children with De Lange and West syndromes.[52] Kawahara et al. reported the effects of rikkushito on gastroesophageal reflux in children with profound neurological impairment.[53]

Three studies examined physical interventions. In a longitudinal open-label study Munakata et al. investigated the effects of black pepper oil at stimulating oral feeding in Costello syndrome and lissencephaly type 1.[54] Mordekar reported treating feed-induced dystonia with parenteral nutrition in Rett syndrome, mucopolysaccharidosis type III and West syndrome.[39] In Rett syndrome, Morton et al. tried a variety of physical interventions to reduce air bloating and apneas at rest, including a large, flattened dummy with a hollow tube to allow the flow of air, gum shield, and palatal training devices.[55] Two of the studies examined psychological interventions. Hyman et al. reported the use of positive reinforcement and guidance techniques in argininosuccinate lyase deficiency, methylmalonyl-CoA mutase deficiency, ornithine carbamoyltransferase deficiency disease and propionic acidemia.[56] Piazza et al. provided training to girls with Rett syndrome in scooping food, bringing food to mouth and placing spoon in mouth by a trainer.[57]

Four of the studies developed or validated tools or scales. Fyfe et al. developed and validated a parent-report checklist and video-based evaluation tool for eating and drinking in Rett syndrome.[58] Iturriaga el al. developed a disability scale for Niemann–Pick type C, which included scoring for feeding difficulties.[59] In 2 studies, de Vries et al. and Lezlezio et al. developed and pilot-validated the TAND Checklist for tuberous sclerosis, which includes a question on feeding difficulties.[25,26] The remaining 24 studies reported the trajectory, incidence and characteristics of the feeding difficulties in this population.

Several studies showed that balloon dilation can be effective for esophageal strictures in epidermolysis bullosa. Percutaneous gastrostomy placement or parenteral nutrition may also reduce feeding difficulties. For drooling, 1 study found that bilateral submandibular gland excision and/or parotid duct ligation may be helpful, but that each patient needed personalized

treatment for it to be effective. For gastroesophageal reflux and emesis, baclofen and rikkushito were found to reduce these symptoms. For oral feeding, black pepper oil may help stimulate appetite and positive reinforcement and training with guidance techniques may be helpful for teaching children with Q3 conditions to feed themselves. One study investigated a flattened dummy with a hollow tube to allow the flow of air, gum shield, and palatal training devices to help reduce air swallowing during feeding in Rett syndrome. None of the studies investigating feeding difficulties are RCTs or systematic reviews, highlighting that higher levels of evidence are needed for this symptom. Some condition-specific tools or scales have been developed and/or validated and may be useful to assess feeding difficulties.

Sleep Disturbance

Sixty-two of the studies investigated sleep disturbance: 38 cross-sectional, 8 RCT, 6 tool/scale development, 5 case-control, 5 case series, 5 surveys, 3 open-label studies, 1 retrospective chart review and 1 systematic review. Sixteen of the studies investigated an intervention, 13 of which were pharmacologic. Twelve studies, including all 8 of the RCTs, investigated melatonin in Rett syndrome,[60–63] 18q deletion syndrome and mucopolysaccharidosis Type III,[64] neuronal ceroid lipofuscinosis type 3,[65] tuberous sclerosis[66,67] and unspecified Q3 Conditions.[68–72] In an open-label study, Ucar et al. investigated risperidone in mucopolysaccharidosis type III.[23] The remaining 2 studies investigated psychological interventions. Piazza et al. reported a case series using a fading procedure in Rett syndrome.[73] In an open-label study, Colville et al. tried a personalized sleep plan developed by a clinical psychologist for children with mucopolysaccharidosis type III.[74] Seven studies developed and/or validated a tool or a scale. De Vries et al. and Lezlezio et al. designed and pilot-validated the TAND Checklist for tuberous sclerosis with a question about sleep disturbance.[25,26] Two studies developed scales with

questions about sleep disturbance in Rett syndrome[27] and Niemann–Pick type C.[59] In unspecified Q3 conditions, Blankenburg et al. and Tietze et al. developed and validated and Maas et al. validated questionnaires on sleep disturbance.[75–77] The remaining 44 studies described the characteristics, trajectory, mechanism and challenges of sleep disturbance.

Clinical practitioners can suggest several interventions that may be effective for sleep problems in Q3 conditions. Melatonin may slightly increase sleep duration and decrease sleep latency, but studies are mixed on its efficacy. Another study shows risperidone prescribed for behavioral problems may also increase sleep. Other non-pharmaceutical interventions, including fading procedures and personalized sleep plans, can also help to decrease sleep disturbances. Sleep problems had the highest number of RCTs of all symptoms but all of them investigated melatonin. Other high-level studies investigating other interventions are necessary. Several studies developed and validated SNAKE for diagnosing sleep disturbances in Q3 conditions, while other condition-specific tools may also be useful for measuring sleep disturbances.

Temperature Regulation

Only 2 studies investigated temperature regulation. In a case-control Svedberg et al. recorded differences in hand temperatures between children with Jacobsen syndrome, spinal muscular atrophy type 1 and other central nervous system damage and healthy controls.[78] In a further case-series, Svedberg et al. tested the efficacy of acupuncture in children with Smith-Lemli-Opitz syndrome and other neurological disorders.[79] Temperature regulation was the least studied symptom. Clinical practitioners could suggest trying acupuncture to caregivers, as 1 study suggests it can raise skin temperature through a cumulative effect. More research is needed for this symptom.

Tone and Motor Problems

Tone and motor problems was the most investigated symptom with 141 studies: 27 case series, 26 tool/scale development, 26 cross-sectional studies, 15 longitudinal, 11 retrospective chart reviews, 7 open-label, 5 surveys, 3 systematic reviews, 3 cohort studies, 3 N-of-1 studies and 2 RCTs. Forty-one of the 141 studies investigated an intervention, 12 of which were pharmacologic. In case-series of Lesch-Nyhan syndrome, Visser et al investigated levodopa or carbidopa[19] and Mizuno et al. compared L-5-Hydroxytryptophan, L-tryptophan and levodopa. Aberg et al. compared levodopa and selegiline in neuronal ceroid lipofuscinosis types 3 and 6 in an open-label trial.[80] Cak et al. investigated how tricyclic antidepressants affect cataplexy in Niemann–Pick type C.[81] In x-linked adrenoleukodystrophy, Hjartarson et al. reported the use of intrathecal baclofen for spasticity and dystonia.[82] Both in ataxia-telangectasia, Zannolli et al. investigated betamethasone in a RCT[83]and Nissenkorn et al. investigated amantadine sulfate in an longitudinal open-label study.[84] In a RCT, Zweije-Horman et al. compared amantadine, fenadrine, madopar and placebo in neuronal ceroid lipofuscinosis type 3.[85] In 18q Deletion syndrome, lissencephaly type 1, metachromatic leukodystrophy and neuronal ceroid lipofuscinosis type 3, Kuhlen et al. reported on the use of dronabinol for spasticity.[86] Liow et al. investigated gabapentin in a cohort study in infantile neuroaxonal dystrophy and dystonia of varying aetiologies.[87] Nava et al. reported the combination of both pharmacologic (botulinum toxin type A) and a physical interventions (serial casting and intensified physical therapy) for equinus deformity in mucopolysaccharidosis type II.[88]

Including Nava et al., 11 studies examined a physical intervention and 9 of these were in Rett syndrome. In case series of Rett syndrome for stereotypic hand movements, Bumin et al. tried hand splints or elbow restraints,[89] Naganuma et al. tried thumb abduction splints,[90] Sharpe et al.

tried elbow orthosis or thumb abduction splints,[91] and Tuten et al. tried hand splints.[92] Also in Rett syndrome, Stasolla et al. used assistive technologies in three studies to increase purposeful hand movements, including picture exchange communication systems compared to vocal output communication aid,[93] wobble microswitch and optic sensors,[94] and photocells, interface and personal computer.[95] Lotan et al. investigated how a daily training treadmill program improved functional skills in Rett syndrome.[96] Mordekar et al reported how switching to parenteral nutrition can improve feed-induced dystonia in Rett syndrome.[39] In Friedrich's ataxia, Ilg examined how video game-based coordinative training can improve coordination.[97]

Fourteen studies investigated a surgical intervention. Eleven of these studies investigated deep brain stimulation in glutaric acidemia type I,[98–100] Lesch-Nyhan syndrome,[98] ataxia-telangectasia,[101] methylmalonyl-CoA mutase deficiency,[101] nemaline myopathy,[101] infantile neuroaxonal dystrophy,[98,100,102–106] and other non-specified Q3 condtions.[107,108] In a retrospective chart review, Buizer reported the used of selective dorsal rhizotomy in lipidoses.[109] In mucolipidosis type II and mucopolysaccharidosis types I, II, III and VI, Haddad et al. investigated the effect of surgery for carpal tunnel syndrome.[110] Van Heest et al. reported on the use of surgery for children with, mucopolysaccharidosis types I, III and VI and carpal tunnel syndrome and trigger digits.[111] Five studies examined at psychological interventions for tone and motor problems and all were in Rett syndrome. In an open-label study, Fabio et al. investigated how selective attention training could reduce stereotypies.[13] In case series, Piazza et al. examined hand function with training in scooping food, bringing food to mouth, and placing spoon in mouth by a trainer[57] and Qvardfordt et al. compared hand function in guided eating to being fed.[112] In case series, Lotan et al. examined daily conductive educational program[113] and Wales et al. tested how different stimulation or attention conditions affected hand stereotypies.[114]

Twenty-six studies developed and/or validated a tool or scale for tone and motor problems. Nine of the studies included tools or scales for neuromuscular diseases that included spinal muscular atrophy type 1. Glanzman et al. developed and validated the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders in 2 studies.[115,116] Krosschell et al. modified and validated the Hammersmith functional motor scale[117] and validated the Test of Infant Motor Performance Screening Items specifically for spinal muscular atrophy type 1. Mazzone et al. compared the reliability of the Hammersmith Functional Motor Scale and the Motor Function Measure-20.[118] Nelson et al. validated the Gross Motor Function Measure[119] and de Lattre et al. and Vuillerot validated the Motor Function Measure.[120,121] Finkel et al. tested the validity of the Test of Infant Motor Performance in children with spinal muscular atrophy type 1.[122] Seven of the studies examined Rett syndrome. Downs et al. tested the use of accelerometers in 2 studies[123,124] and validated the Rett Syndrome Gross Motor Scale in one study.[125] Stahlhut et al. compared the modified two-minute walk test and a modified Rett syndrome specific functional mobility scale.[126] Dy et al. and Fyfe et al. both developed and tested coding protocols for video-taped evaluation of hand steroteypies.[58,127] Mount et al. developed the Rett Syndrome Behaviour Questionnaire that includes questions on hand behaviors.[27] Four studies validated tools or scales in Friedrich's ataxia. Cano et al. and Bürk et al. validated scales to measure the level of impairment due to ataxia[128,129] and Subramony et al. developed and validated a neurologic rating scale.[130] Germanotta et al. validated the use of InMotion Arm Robot to measure upper limb function.[131] Nissenkorn et al. developed a clinical global impression scale for ataxia telangiectasia, which includes sections on motor function.[132] For progressive myelopathy, including mucopolysaccharidosis types I and VI, Castilhos developed and validated the Severity Score System for Progressive Myelopathy.[133] Darling et al. designed and pilot-tested the PKAN-

Disease Rating Scale, which includes a motor examination protocol for infantile neuroaxonal dystrophy.[24] In Niemann–Pick type C, Iturriaga developed a disability scale that includes scoring for motor disorders.[59] Ruiz-Cortes validated the Motor Function Measure in unspecified hereditary neuromuscular diseases[134] and van Capelle developed and validated the Quick Motor Function Test in glycogen storage disease type II.[135] The remaining 48 studies described the characteristics, trajectory and challenges of tone and motor problems in this population.

As the most well studied symptom, there are several pharmacological, physical and surgical interventions for clinical practitioners to consider for the different types of tone and motor problems. Many of the studies investigated the specific stereotypic movements found in Rett syndrome. Interventions for this population include hand or finger splints or elbow restraints, assistive technologies, exercise programs, switching to parenteral nutrition to reduce dystonia and various forms of training or environmental conditions. These studies may not be relevant to other Q3 conditions, as Rett syndrome has distinct tone and motor challenges. In other conditions, several pharmacologic interventions showed some efficacy that clinical practitioners may wish to consider, including levodopa, intrathecal baclofen, tricyclic antidepressants, betamethasone, amantadine sulfate, dronabinol, gabapentin and botulinum toxin type A.

Deep brain stimulation can be considered, but the results are mixed and may depend on condition and even mutation. Other surgical interventions include surgery for carpal tunnel syndrome and selective dorsal rhizotomy to reduce spasticity. Physical interventions include serial casting and intensified physical therapy for equinus deformity and video game training to improve coordination. Only 2 of the studies were RCTs and 3 were systematic reviews, showing the need for higher levels of evidence before strong recommendations for treatment can be made by clinical practitioners. Several studies developed and/or validated scales and tools for tone and

motor problems. Some of the tools, for example a protocol for a video-taped evaluation of hand stereotypies in Rett syndrome, may be condition-specific. However, several tools and scales may be helpful in Q3 conditions to assess and measure tone and motor difficulties.

Urinary Incontinence

Nine studies assessed urinary incontinence: 6 cross-sectional, 2 case-control and 1 survey. All 9 of the studies provided insight into the trajectory or characteristics of the symptom, or compared the severity or features of urinary incontinence to other populations. No evidence on interventions or tools to assess urinary incontinence were found for Q3 conditions. More research is needed for this symptom.

DISCUSSION

This scoping review identified tools to best assess and interventions to best manage troubling symptoms for children living with Q3 conditions. While many of the tools and scales found in this review are condition specific and may not be useful in other Q3 conditions, we did locate some that are either intended for the larger category of Q3 conditions or may be valid in other populations. More research should be done to design tools for symptoms without any current tools and to validate existing tools in Q3 conditions as a whole.

Tone and motor problems was the most investigated symptom. Many of the studies investigated the specific stereotypic movements found in Rett syndrome and these studies may not be relevant to other Q3 conditions. Studies showed some efficacy for a variety of pharmacological interventions, other surgical and physical interventions and mixed results for deep brain stimulation We can only guess as to why tone and motor problems, and specifically the ones associated with Rett syndrome, have been more thoroughly investigated that other symptoms.

One suggestion is that as an outwardly evident symptom, in a clearly diagnosed condition, it is seemingly easier for researchers to investigate.

Behavioural problems were the second most studied symptom, and most of the studies that investigated interventions focused on self-injurious behaviour, particularly in Lesch-Nyhan syndrome. Again, we can only guess as to why self-injury is so well-studied in comparison to other symptoms, but it may be due to the disturbing nature of the symptom for caregivers and the ease at which an investigator can measure changes. No pharmacologic studies showed clear and lasting effects on self-injury, but some behavioral studies provided effective strategies.

Sleep difficulties was the third most studied symptom. Melatonin was overwhelmingly the most studied intervention, but studies were mixed on the efficacy of melatonin in Q3 conditions. Other interventions studies included risperidone prescribed for behavioral problems, fading procedures and personalized sleep plans. Sleep problems had the highest number of RCTs of all symptoms, all of which investigated melatonin.

As the fourth most studied symptom, studies about feeding difficulties investigated a variety of interventions, but several of the studies may only be relevant in epidermolysis bullosa and Rett syndrome. Studies that may be more generalizable to Q3 conditions include, percutaneous gastrostomy placement, parenteral nutrition, bilateral submandibular gland excision and/or parotid duct ligation, baclofen, rikkushito, black pepper oil and behavioral strategies.

Breathing problems were the fifth mostly commonly investigated symptom. Sleep apnea studies in achondroplasia suggest surgical intervention may be necessary, while for other Q3 conditions CPAP or medications, such as naltrexone, appear to be effective. The evidence for other breathing difficulties is mixed and of low quality.

Alertness, constipation, urinary and bowel incontinence and were the fifth, fourth, third and second least studied symptom respectively. For alertness, structured training to increase attention in Rett syndrome was the only intervention studied. For constipation some studies suggest parenteral nutrition, fiber-enriched formula, or supplementation with carnitine. For urinary and bowel incontinence no interventions were studied. The least studied symptom was temperature regulation. Only acupuncture was studied which may increase skin temperature over time.

Overall this scoping review found that very little evidence exists for symptom management in Q3 Conditions. Given the absence of cures for these conditions, the clinical focus should be on symptom management and its contribution to quality of life. We found that most of the studies are concentrated on a handful of diseases, particularly Rett syndrome. Rett syndrome has a distinct clinical profile and interventions used for this condition may not be generalizable to other conditions. Additionally, no condition has a consistent evidence base for all 10 symptoms, and most have only limited evidence for a single symptom. Furthermore, some symptoms, such as temperature regulation problems that have been identified as important to parents, have received little attention in the published clinical research. With the exception of melatonin for sleeping difficulties, there is also a lack of high-level evidence for all symptoms. In conclusion, there is an urgent need for higher levels of evidence for reliable assessment tools and effective interventions for managing prevalent symptoms in Q3 conditions.

Implications for Practice

The studies found in this scoping review are dispersed across multiple disciplines and major general pediatric journals are not represented, except for the *Journal of Pediatrics*. As a result, general pediatricians or even specialists are unlikely to see most of the articles that would

provide valuable evidence to ensure optimal symptom management in this population. Retrieval of this evidence is further complicated by the lack of an accepted and widely used term for this group of progressive, life-threatening conditions. "Q3" is a term used amongst clinicians working with this specific population, but not a term that is reflected in scientific literature and thus a disconnect happens when care providers are looking for evidence of best practices. It is unlikely that a clinician would find these studies through a quick online search. This situation ultimately leaves clinicians with little to no evidence of effective symptoms management for their patients and a distressing inability to improve health outcomes informed by research rather than anecdotal evidence or individual experience.

Limitations and Future Directions

This scoping review is limited by our last search date of January 2018, as more recent studies may have been published within the past year. Additionally, we were not able to translate studies that were not in English or French due to a lack of resources and we were not able to locate the full-text of some studies. This may introduce bias into our results as some studies were excluded before our team had the opportunity to review the full-text. Despite these limitations, it is clear that there needs to be more research done on these symptoms to have a strong evidence base on which to base treatment. For clinical practitioners who must manage the symptoms of child with a Q3 condition with little or no evidence, studies from other conditions may provide the only guidance available for measurement tools and interventions. This scoping review highlights gaps in our knowledge regarding the management of common symptoms in children with neurological, genetic, or chromosome-based conditions that impair quality of life. Researchers and clinicians can use this information to develop broader programs of research to develop

assessment tools and then test interventions that will have a meaningful impact on these children and their families.

Abbreviations

CPAP – Continuous positive airway pressure

OSA – Obstructive sleep apnea

RCT – Randomized controlled trial

Q3 – Quadrant 3

Authorship:

C. Pawliuk developed and implemented the search strategy, reviewed abstracts, titles and full articles, and contributed to the writing of the manuscript and revised it for important intellectual content. K. Widger participated in planning the study, reviewed abstracts, titles and full articles, and revised the manuscript for important intellectual content. T. Dewan participated in planning the study, reviewed abstracts, titles and full articles, and revised the manuscript for important intellectual content. G. Brander implemented the search strategy and revised the manuscript for important intellectual content. H. Brown provided methodological guidance and revised the manuscript for important intellectual content. A.-M. Hermansen reviewed abstracts, titles and full articles and revised the manuscript for important intellectual content. M.-C. Grégoire participated in planning the study, reviewed abstracts, titles and full articles and revised the manuscript for important intellectual content. R. Steele participated in planning the study, reviewed abstracts, titles and full articles and revised the manuscript for important intellectual content. H. Siden conceptualized the study, participated in planning the study, reviewed abstracts, titles and full articles, contributed to the writing and revised it for important intellectual content.

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