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Guidelines for Management of Scoliosis in Rett Syndrome Patients Based on Expert Consensus and Clinical Evidence

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Study Design. Modified Delphi technique.

Objective. To develop guidelines for the clinical management of scoliosis in Rett syndrome through evidence review and consensus expert panel opinion.

Summary of Background Data. Rett syndrome is a rare disorder and clinical expertise is thus with small case series. Scoliosis is a frequent association and the evidence base dealing with scoliosis management in this syndrome is limited. Parents of affected girls and women have expressed needs for more information about scoliosis and Rett syndrome.

Methods. An initial draft of scoliosis guidelines was created based on literature review and open-ended questions where the literature was lacking. Perspectives of four parents of Rett syndrome patients informed this initial draft. Access to an online and a Microsoft Word formatted version of the draft were then sent to an international, multidisciplinary panel of clinicians *via* e-mail with input sought using a 2-stage modified Delphi process to reach consensus agreement. Items included clinical monitoring and intervention before the diagnosis of scoliosis; monitoring after the diagnosis of scoliosis; imaging; therapy and conservative management; bracing; and preoperative, surgical, and postoperative considerations.

Results. The first draft contained 71 statements, 65 questions. The second draft comprised 88 items with agreement to strong agreement achieved on 85, to form the final guideline document. A comprehensive, life-span approach to the management of scoliosis in Rett syndrome is recommended that takes into account factors such as physical activity, posture, nutritional and bone health needs. Surgery should be considered when the Cobb angle is approximately 40° to 50° and must be supported by specialist management of anesthesia, pain control, seizures, and early mobilization.

Conclusion. Evidence- and consensus-based guidelines were successfully created and have the potential to improve care of a complex comorbidity in a rare condition and stimulate research to improve the current limited evidence base.

Key words: Rett syndrome, scoliosis, neuromuscular diseases, Delphi technique, practice guideline. **Spine 2009; 34:E607–E617**

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Rett syndrome is a rare neuromuscular disorder defined clinically by a set of criteria in 1988.[1] The identification of a link with a MECP2 gene abnormality[2] led to further diagnostic criteria modifications in 2002.[3] The syndrome primarily affects women, results in severe intellectual disability and functional dependence, and is associated with comorbidities such as seizures,[4] nutrition and growth problems,[5] autonomic disturbances,[6,7] and osteoporosis.[8] Scoliosis (of neuromuscular type) is the most common orthopedic condition.[9–11] Onset of scoliosis before adolescence is not unusual, with data in our population-based Australian Rett Syndrome Database finding that the median age of onset for scoliosis is 9.8 years with about 75% affected by the age of 13 years.[12] Like other types of neuromuscular scoliosis, the curves in these patients progress more rapidly than idiopathic scoliosis, on average 14° to 21° per year in small case series,[13–15] and may not necessarily halt with skeletal maturity.[14] There may be adverse effects such as pain, loss of sitting balance, deterioration of walking skills, and progressive restrictive lung disease.[16]

The evidence base for scoliosis management in Rett syndrome is limited. Some case series[11,15,17,18] and

one case study[19] are available which can be supplemented by narrative reviews for neuromuscular scoliosis.[16,20,21] For example, expert opinion from 2 sources suggests that planning for surgery should commence when the Cobb angle is greater than 40° to 60°.[18,20] Clinical trials in neuromuscular scoliosis are limited, to date focusing on blood loss reduction.[22,23] As Rett syndrome is rare,[24] clinicians usually have exposure to small patient series.

Parents are integral to the management of scoliosis in Rett syndrome and can offer perspectives on management.[18,25] Several families participating in the population-based Australian Rett Syndrome study[24] had voiced concerns to researchers about lack of available information on scoliosis management. This led to the current project, which included a review of the literature and the use of collective expertise of an international group of experienced clinicians and input from family members. A consensus building process was employed using a modified Delphi technique[26] with the aim of increasing understanding and developing consensus guidelines for the clinical management of scoliosis in Rett syndrome.

■ Materials and Methods

This project took the format recommended for the development of clinical guidelines by the National Health and Medical Council[27] and the Royal College of Pediatrics and Child Health.[28] The project was directed from the Telethon Institute for Child Health Research, Western Australia from 2006 to 2008 and was approved by the Ethics Committee of Curtin University of Technology.

Literature Review and Parent Perspectives

A literature search was performed. Databases included PubMed, Medline, the Cochrane Library, EMBASE, CINAHL, PsychINFO, and Web of Science; online libraries included those of the World Health Organization, CMA–Clinical Practice Guidelines, Geneva Medical Research, the National Guideline Clearinghouse, National Electronic Library for Health, Scottish Intercollegiate Guidelines, the British Orthopedic Association, National Institute for Health and Clinical Excellence, and the Trip Database. Search and key words included Rett syndrome, comorbidity, physiotherapy, scoliosis, predictors, bracing, anesthesia, surgery, outcome, neuromuscular, management, complications, orthopedic, and techniques. The search was limited to English and the years 1980 to 2007. If the title and abstract described the management of neuromuscular scoliosis, the full article was retrieved. Statements describing clinical management of scoliosis in Rett syndrome were extracted from the full text.

Rettnet, an online e-mail information interchange for parents/persons with a Rett syndrome interest,[29] was used to collect parent and caregiver perspectives. Using the filter word "scoliosis" for postings between March 2001 and October 2006, interchange regarding scoliosis management were extracted.

Initial Guideline Development, Expert Panel Recruitment, and Guideline Redrafting Using the Modified Delphi Process

Referenced statements extracted from the literature and Rettnet postings were categorized into topic areas. These were accompanied by a 5-point Likert scale for agreement rating (strongly agree, agree, neither agree or disagree, disagree, strongly disagree) with space for comments. If there was no literature, an open-ended question on management was constructed. The statements and questions were listed in a Microsoft Word document format and an online version created using HTML form and PHP script. Participants could indicate their level of agreement with dropdown menus and type in comments in the spaces provided, and responses could be saved, edited, and submitted in stages. Data received were stored in a MySQL database (Sun Microsystems, Inc., Cupertino, CA) on a secured server located at the Telethon Institute for Child Health Research.

Clinicians with Rett syndrome experience from different countries in the disciplines of orthopedics, spinal surgery, pediatrics, pediatric neurology, clinical genetics, anesthesia, nursing, physical and occupational therapy were identified, and through networks of researchers, publications and the Australian Rett Syndrome[24] and InterRett[30] databases. A Rettnet request was posted for parents to recommend clinicians with appropriate expertise. Snowball sampling using collegial recommendations was used to expand the sample. Parents who were participants in the Australian Rett Syndrome and InterRett studies were identified. Potential participants were contacted by telephone or e-mail to request their participation; English was the language used. Seventy-two of the 128 identified clinicians were successfully contacted. Sixty (83.3%) agreed to participate as the expert panel, along with a parent from 4 affected families.

For the first round of the Delphi process, members of the expert panel provided feedback on the e-mailed Microsoft Word document or online version, which was username and password protected. Panel members were directed to respond to nominated sections relevant to their professional scope, for example, only orthopedic surgeons were required to respond to the statements and questions on imaging. A predetermined level of consensus was established: consensus was attained where a minimum of 70% of responses were within one response category of the median response.

The second guideline set was informed by these responses and sent for second round consensus assessment. Any returned comments were considered for inclusion. This process was a modified Delphi process because consensus after round 2 was in the main clear and therefore we did not send panel members their previous responses together with the median responses for the group. The statements were then summarized to reduce repetition and sent to the panel for final endorsement. Some final discussion points were incorporated into the endorsed document depending on consensus. A level of evidence using the Scottish Intercollegiate Guidelines Network grading scheme[31] was applied to each item for which there was consensus: level 1 representing evidence from systematic reviews and randomized controlled trials, level 2 case control or cohort studies, level 3 case reports or case series, and level 4 expert opinion.

Table 1. Agreement With Items Describing the Monitoring and Intervention Before Diagnosis of Scoliosis*

Items Describing Monitoring and Intervention Before Diagnosis (Reference and Study Design)	Level of Evidence (SIGN)	Median Response	n/N (%) With Median Response or 1 Category Either Side
All children with a clinical diagnosis of Rett syndrome should have a molecular test as genotype may influence the development and management of scoliosis (cohort study[12])	2+	Agree	9/9 (100.0)
Children with abnormal early development and those who never learned to walk have been shown to be at higher risk of developing scoliosis. These children require closer monitoring (cohort study[12]; case series[14])	2+	Strongly agree	9/9 (100.0)
A physical assessment of the spine should be conducted at the time of diagnosis of Rett syndrome	4	Strongly agree	9/9 (100.0)
A physical assessment of the spine should be conducted at least every 6 mo after diagnosis of Rett syndrome	4	Agree	7/9 (77.8)
Develop, maintain and promote walking for as long as possible (case series[17]; case series[32])	3	Strongly agree	9/9 (100.0)
It is important to maintain strength of the back extensors (case series[14])	3	Agree	9/9 (100.0)
It is important to maintain flexibility of the spine (case series[14])	3	Strongly agree	9/9 (100.0)
It is important to implement a postural management scheme that includes appropriate support for correct sitting posture	4	Strongly agree	9/9 (100.0)
It is important to implement a postural management scheme that includes sleeping posture supports	4	Agree†	9/9 (100.0)
Because of the high prevalence of scoliosis in Rett syndrome, families should be given information about this early in the child's clinical course (narrative review[33])	4	Strongly agree	8/9 (100.0)

*All items completed by 9 physicians and therapists.
†1 strongly agree, 4 agree, and 4 neither agree nor disagree = therefore although there is consensus, this is the weakest of the items and therefore we feel more caution recommending this strategy.
SIGN indicates Scottish Intercollegiate Guidelines Network.[31]

■ Results

Literature Review and Parent Perspectives

Search of 16 databases revealed 1080 citations as potentially relevant. Of these, 183 articles were retrieved and reviewed in full text from August 2006 to March 2008: 42 supported the final guideline draft. No randomized controlled trials concerning neuromuscular scoliosis management were found.

Three-hundred and nine Rettnet postings relating to scoliosis management were found with some families sending multiple postings. Common themes included conservative prevention of scoliosis progression, difficulties with spinal bracing, medical issues associated with severe scoliosis, anxiety about pending surgical procedures, and a need for more preoperative information and surgical outcomes.

Expert Panel Participation

Of the 60 clinicians agreeing to participate, 40 (66.7%) were orthopedic or spinal surgeons, 6 (10.0%) worked in areas of child neurology or developmental pediatrics, and there were 8 (13.3%) physiotherapists or occupational therapists, 2 (3.3%) anesthesiologists, 2 (3.3%) clinical geneticists, 1 (1.7%) pediatric endocrinologist, and 1 (1.7%) spinal nurse.

Forty-one participants responded, including 25 (61.0%) orthopedic surgeons, 7 (17.1%) physical or occupational therapists, 4 (9.8%) child neurologists or developmental pediatricians, 2 (4.9%) anesthesiologists, 2 (4.9%) clinical geneticists, and 1 pediatric endocrinologist (2.4%). Nearly half (46%) were North American (46%), 11 (26.8%) were European, 9 (22.0%) were Australian with 1 (2.4%) from Israel. With regards to patients managed, 19 (54.3%) had managed more than 20, 8 (22.8%) 11 to 20 patients, 5 (14.3%) 6 to 10 patients, and 3 (8.6%) clinicians had managed less than 5 Rett syndrome patients.

Initial Guideline Draft and Redrafting Using the Modified Delphi Process

The initial guideline draft comprised the following sections: monitoring and intervention before the diagnosis of scoliosis; monitoring and intervention after the diagnosis of scoliosis; imaging; therapy; bracing; preoperative considerations; perioperative considerations; and postoperative considerations. It included 71 statements, 65 questions and a reference list, and all of the Rettnet topics were represented.

Thirty-seven of 41 (90.2%) clinicians responded to the first round. Three of the 4 parents also responded and found that the scope of the document was satisfactory and relevant to their experiences. Thirty-eight (92.7%) clinicians responded to version 2, which comprised 92 items. The final guidelines document comprised 85 separate statements with agreement or strong agreement. Tables 1 to 4 list the items, together with levels of evidence, the median responses, and the percentage of responses within one category of the median.

Two items were changed in response to comments received in the second round. Consensus was achieved for the item stating a preference for a single-stage surgical approach (Table 4, item 16). We elected to expand this after discussion to "If extensive anterior-posterior surgery is planned, then consideration should be given to staging the procedure to reduce the risk of complications particularly if the child has significant comorbidities."[54,56] No consensus was

Table 2. Agreement With Items Describing the Monitoring After Diagnosis of Scoliosis* and Imaging of Scoliosis†

Items Describing Physical Monitoring After Diagnosis of Scoliosis (Reference and Study Design)	Level of Evidence (SIGN)	Median Response	n/N (%) With Median Response or 1 Category Either Side
Referral should be made to an orthopedic surgeon when there is clinical concern regarding scoliosis (case series[11]; narrative review[33])	3	Strongly agree	30/30 (100.0)
Scoliosis monitoring should be conducted every 6 mo (narrative review[33])	4	Agree	25/30 (83.3%)
Scoliosis monitoring should be more frequent when there is evidence of low muscle tone		*Neither agree or disagree*	*23/30 (76.7)*
Scoliosis monitoring should be more frequent when there is evidence of limited early development of mobility	4	Agree	22/30 (73.3)
Scoliosis monitoring should be more frequent during growth spurts	4	Agree	26/29 (89.6)
Scoliosis monitoring should be more frequent when the curve is progressing rapidly	4	Strongly agree	27/30 (90.0)
Children with genotypes known to be at higher risk of more severe scoliosis (p.R168X, p.R255X, p.R270X) require more frequent monitoring (cohort study[12])	2	Agree	27/30 (90.0)
Relative importance of factors that determine the frequency of orthopedic assessment include	4		N (%) ranking in the top 5
Progression of the curve			26/28 (92.8)
Age of onset			22/28 (78.0)
Cobb angle			21/28 (75.0)
Skeletal maturity			17/28 (60.7)
Level of ambulation			15/28 (53.6)
Genotype			13/28 (46.4)
Current age			12/28 (42.8)
Level of lung function			10/28 (35.7)
Muscle tone			9/28 (32.1)
Pattern of the curve			6/28 (21.4)
Physical assessment in Rett syndrome should include symmetry of weight bearing in sitting (narrative review[16])	4	Agree	29/30 (96.7)
Physical assessment in Rett syndrome should include level of walking ability including time spent walking and total distance walked	4	Agree	30/30 (100.0)
Physical assessment in Rett syndrome should include sitting balance (narrative review[16])	4	Agree	29/30 (96.7)
At each visit, weight should be measured (narrative review[34])	4	Agree	28/30 (93.3)
At each visit, height should be measured (n = 29) (narrative review[34])	4	Agree	27/30 (93.1)
Due to the potential to lose height, the height of girls with Rett syndrome should be measured in the supine position		*Neither agree or disagree*	*25/30 (83.3)*
Items describing imaging (reference and study design)			
Request an initial x-ray if there is evidence of a curve (narrative reviews[35,36]; reliability studies[37,38])	4	Strongly agree	21/21 (100.0)
Six monthly follow-up x-rays are suggested if the Cobb angle is more than 25° before skeletal maturity (narrative reviews[20,39])	4	Strongly agree	16/21 (76.2)
12 monthly x-rays are required after skeletal maturity (narrative review[16])	4	Agree	17/21 (81.0)
Plain radiography is sufficient in monitoring the progression of the curve (narrative reviews[16,36])	4	Strongly agree	20/21 (95.2)
Standing upright anteroposterior and lateral spinal radiographs are advised for patients at their initial visit (narrative reviews[16,21])	4	Strongly agree	20/21 (95.2)
Sitting upright anteroposterior and lateral spinal radiographs are advised for patients who cannot stand (narrative reviews[16,21])	4	Strongly agree	21/21 (100.0)
Supine anteroposterior and lateral spinal radiographs are advised for patients who cannot sit	4	Agree	19/21 (90.5)
Anteroposterior films alone may be used in follow-up x-rays (narrative review[34])	4	Agree	17/21 (81.0)
A hand and wrist radiograph can be taken to assess skeletal maturity (descriptive text[40])	4	Agree	20/21 (95.2)

Items in italics dropped because of no consensus direction.
*Items completed by 30 orthopedic surgeons, physicians, and therapists.
†Items completed by 21 orthopedic surgeons.
SIGN indicates Scottish Intercollegiate Guidelines Network.[31]

achieved for the pain control regimen (Table 4, item 29), as it was noted that medication regimens constantly change. In the final document, this was replaced with the more general statement "Postoperative analgesia must be closely monitored by a specialist pain team with 24-hour cover."[54]

The final guideline document was summarized to reduce repetition and was endorsed by 35 panel members (Table 5). At this stage, some orthopedic panel members wished to identify additional detail of the role of pelvic fusion in relation to the amount of pelvic obliquity and whether the patient was ambulatory. However, as many different views were expressed during this discussion, the original statements were retained (Table 4, items 20 and 21).

■ Discussion

This project integrated available evidence in the literature with parental input and expert clinician consensus using a modified Delphi technique. The resulting

Table 3. Agreement With Items Describing Therapy for Scoliosis* and Spinal Bracing†

Items Describing Therapy for Scoliosis (Reference and Study Design)	Level of Evidence (SIGN)	Median Response	n/N (%) With Median Response or 1 Category Either Side
Commence therapy as soon as there is clinical concern (case study[19])	3	Strongly agree	9/9 (100.0)
Physiotherapy should be used to maintain general well-being in children with Rett syndrome and scoliosis (narrative reviews[16,21])	4	Agree	9/9 (100.0)
Physiotherapy will not prevent the progression of an established scoliosis (narrative reviews[16,21])	4	Agree	9/9 (100.0)
Aim to increase the distance that the child can walk	4	Agree	9/9 (100.0)
Aim to increase the length of time that the child is able to stand on her feet	4	Agree	9/9 (100.0)
Aim for walking and/or standing at least 2 hr per d (case study[19])	3	Agree	9/9 (100.0)
For those who cannot walk, support standing in a standing frame or at least 30 min a d	4	Agree	9/9 (100.0)
Aim to maintain range of movement of joints (case series[17]; case study[19]; narrative review[21])	4	Strongly agree	9/9 (100.0)
Symmetrical supported seating is valuable for the child's comfort and functioning (narrative reviews[21] case series[17] before and after study[41])	3	Strongly agree	9/9 (100.0)
Time spent in daylight, and/or supplements of vitamin D should be considered to promote bone health (narrative review[42])	4	Agree	10/10 (100.0)
Improving dietary intake of calcium should be considered to promote bone health (RCTs[43,44])	1+	Agree	10/10 (100.0)
In severe scoliosis where surgery is not indicated, the management plan should include the provision of supported sitting to optimize posture-(Holmes et al 2003–before and after study[41])	3	Strongly agree	9/9 (100.0%)
In severe scoliosis where surgery is not indicated, the management plan should include the monitoring and treatment of pressure sores	4	Strongly agree	9/9 (100.0)
In severe scoliosis where surgery is not indicated, the management plan should include chest physiotherapy, flu immunization, and a low threshold for antibiotic use to minimize the effects of restrictive lung disease	4	Agree	9/9 (100.0)
Items describing spinal bracing for scoliosis (reference and study design)			
There is no consensus that spinal bracing is beneficial in reducing the progression of scoliosis in Rett syndrome (case series[11,13,45]; narrative reviews[16,21]; narrative[18])	3	Agree	28/31 (90.3)
A brace is warranted in a very severe case of scoliosis where the child cannot sit up straight (case series[51])		*Neither agree or disagree*	*27/31 (90.0)*
A brace is warranted where active seating and trunk activation cannot be achieved (case series[51])	3	Agree	30/31 (96.8)
If tolerated, bracing should be used in the skeletally immature child to delay surgery (narrative reviews[16,21]; narrative[18])	4	Agree	29/31 (93.5)
The following are potential complications of bracing:		Agree	30/31 (96.8)
Pressure sores	4		
Respiratory impairment (case series[16,18])	3		
Discomfort (case series[28])	3		
Skin irritation	4		
Potential to decrease physical activity (case series[28])	3		

Item in italics dropped because of no direction to the consensus.
*Items completed by 9 physicians and therapists, items 10 and 11 also completed by a pediatric endocrinologist.
†Items completed by 31 orthopaedic surgeons and therapists.
SIGN = Scottish Intercollegiate Guidelines Network.[31]

guideline contains statements relevant to the development and progression of scoliosis in Rett syndrome, including monitoring as well as conservative and surgical interventions. This document is comprehensive with a life-span approach.

We initiated the study in response to the voiced concerns of parents who had many questions about the management of scoliosis and many of whom have felt that the provision of information about scoliosis management was poor.[25] Incorporating parental concerns renders these guidelines reflective of consumer needs and supports their social validity.[63] Guidelines are systematically developed statements that assist clinicians and patients to engage in best practice.[26] Scoliosis management requires contributions from professionals with medical, surgical, and therapy skills. For that reason, a multidisciplinary panel was sought. Although "drop out" did occur, the number of participants and cross section of professions was reasonable. We acknowledge that anesthesiologists and nurses were under represented, which should be addressed during future guideline revisions. Of those who participated, responses were high and many constructive comments were received. Use of the internet and e-mail enabled timely worldwide consultation. The method employed allowed time for considered responses. A lack of face-to-face contact can be both advantageous in allowing freedom of expression with reduction of group pressures and disadvantageous in that it restricted constructive debate over contentious issues such as the management of pelvic obliquity.[26]

A significant limitation of this project is that the peer-reviewed literature is very limited and even though expert exposure is also small, the consensus of experts played a particularly important role. This document is thus a current best effort to provide practitioners with guidance in the management of an important orthopedic condition in this rare disorder.

Table 4. Agreement With Items Describing the Preoperative*; Perioperative†; and Postoperative Considerations‡

Items Describing Preoperative Considerations (Reference and Study Design)	Level of Evidence (SIGN)	Median Response	n/N (%) With Median Response or 1 Category Either Side
A surgical objective is the restoration of the normal sagittal profile (narrative reviews[16,21,34])	4	Agree	19/21 (90.5)
A surgical objective is to achieve level shoulders and hips (narrative reviews[21])	4	Agree	20/21 (95.2)
A surgical objective is to achieve a spine that is balanced and fused (narrative review[34])	4	Strongly agree	21 (100.0)
Surgery should be performed when the Cobb angle is approximately 40°–50° (case series[18,46,47]; narrative review[20])	3	Agree	18/21 (85.7)
Sitting balance is an important consideration when planning surgery for scoliosis in Rett syndrome (narrative review[21])	4	Strongly agree	19/20 (95.0)
Where there is a severe anesthetic risk of complications, surgery should be performed at a specialist centre	4	Strongly agree	21/21 (100.0)
Caution should be used when performing surgery in younger children due to the following problems: decreased trunk height, pulmonary restriction, "crankshaft" phenomenon, secondary curvatures	4	Agree	20/21 (95.2)
Surgery should not be delayed until skeletal maturity has been achieved (narrative review[20])	4	Agree	16/20 (80.0)
Items describing perioperative considerations (reference and study design)			
There should be a period of preoperative hyperalimentation if weight is less than the 5th centile (narrative review relating to cerebral palsy[48])	4	Agree	24/25 (96.0)
The following markers of nutrition should be assessed:			
Body mass index	4	Agree	21/25 (84.0)
Haemoglobin	4	Agree	25/25 (100.0)
Electrolytes	4	Agree	25/25 (100.0)
Albumin (narrative review[21])	4	Agree	25/25 (100.0)
White cell count (narrative review[21])	4	Agree	23/25 (92.0)
Given the higher incidence of decreased bone density in children with Rett syndrome, bone density should be assessed pre-operatively (n = 26)–(cohort study8)		*Neither agree or disagree*	*25/26 (96.2)*
Patients with Rett syndrome need special anaesthetic consideration in line with other neuromuscular disorders. They are highly sensitive to analgesia, sedatives, and volatile anesthetics (case studies[49–51];case control study[52])	2-	Agree	21/21 (100%)
In addition to the preoperative assessment used in all scoliosis surgery, the following must be considered before anaesthetizing a child with Rett syndrome:			
Breathing patterns (narrative reviews[16,21])	4	Agree	23/25 (92.0)
Excess salivation (n = 24)	4	*Neither agree or disagree*	*24/24 (100.0)*
Gastrooesophageal reflux (n = 24)(narrative reviews[20,21])	4	Agree	23/24 (95.8)
Autonomic disturbance	4	Agree	20/25 (80.0)
Seizure history and management (narrative review20)	4	Agree	24/25 (96.0)
Preoperative ECG (narrative review[21]) to diagnose prolonged QT syndrome	4	Agree	23/25 (92.0%)
A Bispectral Index Monitor should be used in inducing and maintaining an adequate level of anesthesia in children who are extremely sensitive to anaesthetic agents (case studies[49,50])		*Neither agree or disagree*	*25/25 (100.0)*
If a reliable signal can be obtained, MEPs and/or SSEPs can be used to detect neurological injury during neuromuscular scoliosis surgery (case series[5,23,36,53]; narrative reviews[20,21,54])	3	Agree	25/26 (96.2)
A posterior only fusion should be the definitive management of neuromuscular scoliosis in girls with Rett syndrome (narrative reviews[21])	4	Agree	21/25 (84.0)
Both an anterior and posterior approach achieves maximal surgical correction and stability (narrative reviews[21])	4	Agree	22/25 (88.0)
In the majority of cases, it will be possible to use a posterior approach to spinal surgery (case series[55])	3	Agree	24/25 (96.0)
If anteroposterior surgery must be used, a single stage approach is preferable to reduce surgical insult (retrospective case series relating to cerebral palsy[56])	3	Agree	23/26 (88.5)
Fixation to the pelvis is undesirable in patients who are ambulant (narrative reviews[16,21])	4	Agree	21/24 (87.5)
If pelvic obliquity exists and the child is nonambulant, pelvic fixation is indicated (narrative review[16,21])	4	Agree	23/25 (92.0)
There may be a role for halo-femoral traction intra-operatively in large, rigid curves (retrospective case control study[57]; retrospective prospective quasi-experimental study58)		*Neither agree or disagree*	*22/25 (88.0)*
Items describing postoperative considerations (reference and study design)			
Postoperatively, the following should be assessed as a measure of surgical success:			
Complications including bleeding, infection and duration of ICU stay (narrative reviews[16,20]; case series[56,47,59])	3	Agree	23/25 (92.0)
Cobb angle and achievement of fusion (narrative review[16] retrospective case series[59])	3	Agree	22/24 (91.7)
Respiratory status (narrative[20]; retrospective case series[59])	3	Agree	23/23 (100.0)
Sitting balance, function and quality of life (narrative review[16]; before and after study[16,60]; descriptive study[61]	3	Strongly agree	25/25 (100.0)
Parental satisfaction (narrative reviews[16,20])	4	Agree	25/25 (100.0)
Weight gain		*Neither agree or disagree*	*24/25 (96.0)*
Admit to HDU/ICU postoperatively (n = 27) (narrative review[20]; narrative review relating to cerebral palsy[48])	4	Strongly agree	25/27 (97.2)

(*Continued*)

Table 4. Continued

Items Describing Preoperative Considerations (Reference and Study Design)	Level of Evidence (SIGN)	Median Response	n/N (%) With Median Response or 1 Category Either Side
Care needs to be taken with regards the titration of analgesia so that pain relief is adequate, sedation is minimized and to ensure respiratory effort is not compromised (consensus guidelines62)	4	Strongly agree	26/27 (96.3)
Frequent and aggressive chest physiotherapy should be used	4	Agree	31/31 (100.0)
A clear management plan should be constructed when the patient is transferred back to the ward	4	Strongly agree	33/33 (100.0)
Seek expert advice to optimize nutritional status	4	Agree	26/26 (100.0)
IV paracetamol 15 mg/kg, 6/24 Ketamine infusion 0.1–0.2 mg/kg/h to reduce opioid requirements, Morphine 10–20 μg/kg/h or Tramadol 0.25–0.33 mg/kg/h (if respiratory depression a major concern and seizures are adequately controlled and/or are absence type or are not present), Diazepam 0.025–0.075 mg/kg 6/24 for muscle spasm management, pain team review twice daily, 24 hr cover for review prn if deteriorates		*Neither agree or disagree*	*23/24 (95.8)*
Consult parents or caregivers to help assess the child postoperatively (narrative review[18])	4	Strongly agree	30/30 (100.0)
Log roll for bed mobility	4	Agree	29/29 (100.0)
Sit over the edge of the bed on the first postoperative day	4	Agree	31/31 (100.0)
Transfer to a chair on the second postoperative day	4	Agree	30/31 (96.8)
Walking (if possible) on the third postoperative day	4	Agree	29/30 (96.7)
Postoperative reviews should be carried out at 6 wk and then every 2/3 mo over the first yr	4	Agree	24/25 (96.0)
After 1 yr, reviews should be carried out annually	4	Agree	24/25 (96.0)

Items in italics dropped because of no direction to the consensus.
*Items completed by 21 orthopedic surgeons.
†Items completed by 25 orthopedic surgeons, anesthesiologists, and physicians. One pediatric endocrinologist also answered item 3.
‡Items completed by 25 orthopedic surgeons, anesthesiologists, and physicians with 7 therapists completing questions relating to therapy.
SIGN = Scottish Intercollegiate Guidelines Network.[31]

There are usually different ways to manage a clinical problem and the many comments we received reflected the variety of clinical practice. For example, the panel endorsed use of 6 monthly anteroposterior radiograph films to assess the progress of scoliosis but some members of the panel requested both anteroposterior and lateral radiograph films at 12 monthly intervals in their practice. Similarly, use of the supine position for radiographs was recommended for girls who cannot sit but some clinicians commented that the supine position was preferred for all cases because the measures were felt to be more reproducible. The scoliosis guidelines therefore represent guidance and discussion points rather than a specific recipe for clinical management.

The clinical experience of our panel matched the consumer experience of a group of 168 parents with a daughter with Rett syndrome who described their perception of effectiveness of treatments for scoliosis in an online questionnaire. Parents judged bracing effective in delaying the need for surgery in a minority of cases with its use tempered by commonly experienced adverse effects, and physiotherapy was considered beneficial to quality of life in nearly two-thirds (62%) of cases countered by comments relating to the lack of effect on the progression of the scoliosis.[12,25] This highlights the importance of involving parents, who have a wealth of knowledge, understanding and experience with both Rett syndrome and scoliosis, in health care. They are crucial partners in this process.[18]

Consistent with earlier recommendations in the literature,[18,46,47] surgery should be considered when the Cobb angle is approximately 40° to 50°. Surgical intervention before the development of severe scoliosis and before the effects of other comorbidities (such as decreasing mobility with increasing age in Rett syndrome[64]) come into play, has the potential to improve surgical outcomes. This recommendation is also a measurable outcome of the acceptance of these guidelines by the orthopedic community.

There is clearly a need for additional research. As case series to date have been small, multi-institutional study would better represent the population. Promisingly, Lotan *et al*[19] found improvement in the Cobb angle in response to an intensively structured physical therapy environment for one subject but this needs to be replicated in larger samples to check effectiveness. Larger samples would also permit subanalysis of predictive factors of age of onset, genotype, preceding mobility level, and severity of Cobb angle. Other issues that could be assessed include establishment of a relationship between supine and standing radiographs, the impacts of spinal bracing and physical therapy, timing and type of surgery (the latter relevant to optimal surgical approaches and cases with pelvic obliquity), postoperative pain and respiratory interventions, and postsurgical complications and outcomes. Strategies for support after the immediate postoperative period have not been determined in these guidelines and this is another important subject for further research.

The authors, along with an international clinical panel, successfully created guidelines for treating scoliosis in Rett syndrome where no prior document existed. The project was a response to parental needs and used innovative methodology. The recommendations

Table 5. Final Guidelines Endorsed by the Expert Panel for the Management of Scoliosis in Rett Syndrome

Monitoring and intervention before diagnosis of scoliosis
All children with a clinical diagnosis of Rett syndrome should undergo genetic testing as genotype may influence the development and management of scoliosis
Because of the high prevalence of scoliosis in Rett syndrome, families should be given information about this early in the child's clinical course
Physical assessment of the spine should be conducted at the time of diagnosis of Rett syndrome and at least every 6 mo thereafter
Therapy should aim to:
- Develop, maintain, and promote walking for as long as possible
- Optimize strength of back extensors
- Maintain flexibility of the spine
- Implement a postural management scheme that includes appropriate support for correct sitting posture and sleeping posture supports

Monitoring after a diagnosis of scoliosis
- Referral should be made to an orthopedic surgeon when there is clinical concern regarding scoliosis
- Physical examination of the spine should be conducted at least every 6 mo, but the frequency of assessment should be increased in the following situations:
  - Abnormal early development/never learning to walk
  - Low muscle tone
  - During growth spurts
  - Early age of onset
  - Greater Cobb angle
  - Children with genotypes known to be at higher risk of more severe scoliosis (p.R168X, p.R255, p.R270X)
- Physical assessment in Rett syndrome should include:
  - Sitting balance and symmetry of weight bearing in sitting
  - Level of walking ability and time spent walking
  - Total distance walked
- At each visit, height and weight should be measured

Imaging
- Request an initial x-ray if there is evidence of a curve
- It is preferable to assess skeletal maturity with a hand and wrist radiograph but assessment of the iliac crest growth plate is also an option
- Six monthly x-rays are suggested if the Cobb angle is more than 25° before skeletal maturity and 12 monthly x-rays after skeletal maturity until evidence of no further progression
- Plain radiography is sufficient in monitoring the progression of the curve. The following views should be obtained and should include shoulder to pelvis:
  - Standing upright AP and lateral spinal radiographs for patients who can stand at their initial visit
  - Sitting AP and lateral spinal radiographs for patients who cannot stand
  - Supine AP and lateral spinal radiographs for patients who cannot sit
- AP films alone may be used in follow-up x-rays

Therapy and conservative management
- Involve physiotherapists and occupational therapists as soon as scoliosis has been diagnosed
- Physiotherapy should be used to maintain musculoskeletal well-being in children with Rett syndrome and scoliosis. There is not yet evidence that physiotherapy will prevent progression of an established scoliosis
- Aim to prolong ambulation as long as possible. Aim to increase the distance that the child can walk and/or the length of time the child can stay on their feet (at least 2 hr per d where possible)
- For those who cannot walk, use standing frames for at least 30 min a d
- Aim to maintain range of movement of joints
- Symmetrical seating is valuable for the child's comfort and functioning
- Assess, monitor, and optimize Vitamin D levels. Improve dietary intake of calcium and time spent in daylight to promote bone health
- In severe scoliosis where surgery is not indicated, the management plan should include:
  - The provision of supported seating to optimize posture
  - Monitoring and treatment of pressure sores
  - A low threshold for antibiotic use during respiratory infections to minimize the effects of restrictive lung disease

Spinal bracing
- There is no consensus that bracing is beneficial in reducing the progression of scoliosis in Rett syndrome but it may used if seating and trunk activation cannot be achieved
- If tolerated, bracing should be used in the skeletally immature child, to help delay surgery
- The following potential complications of bracing must be considered: pressure sores, respiratory impairment, discomfort, skin irritation, exacerbation of gastroesophageal reflux, and the potential to decrease trunk strength, flexibility, and physical activity

Preoperative considerations
- Surgery should be performed in a specialist center due to the high risk of anesthetic and postsurgical complications
- Surgery should not be delayed until skeletal maturity has been achieved, however, caution should be used before performing surgery in children younger than 10 yr of age due to the following problems: decreased trunk height, pulmonary restriction, "crankshaft," and secondary curvatures
- Surgery should be considered when the Cobb angle is approximately 40°–50°
- Surgical objectives should include:
  - Achieving a spine that is balanced and fused
  - Restoration of the normal sagittal profile
  - Achieving level shoulders and hips
  - Improving the well-being and functioning of the child
  - Improving carer well-being
- There should be a period of hyperalimentation if weight is less than the 5th centile
- The following markers of nutrition should be assessed: BMI, hemoglobin, electrolytes, albumin (<3.5 mg/dL), white cell count
- Patients with Rett syndrome need special anesthetic consideration in line with other neuromuscular disorders. They are highly sensitive to analgesia, sedatives, and volatile anesthetic agents

(*Continued*)

Table 5. Continued

In addition to the preoperative assessment used in all scoliosis surgery, the following must be considered before anaesthetizing a child with Rett syndrome:
Breathing patterns (hyperventilation, breath holding)
Preoperative arterial blood gases/capillary gases
Gastroesophageal Reflux
Autonomic disturbance
Seizure history, management, and medications
Preoperative ECG to identify possible prolonged QT syndrome
Surgical considerations
In the majority of cases it will be possible to use a posterior-only spinal fusion. This is the definitive management of neuromuscular scoliosis in girls with Rett syndrome
If anteroposterior surgery must be used, a single-stage approach is preferable to reduce anesthetic and surgical complications but a staged procedure may be appropriate in the presence of significant co-morbidities
Fixation to the pelvis is indicated if pelvic obliquity exists in the nonambulant child. There is no consensus about the degree of obliquity that indicates fixation
If a reliable signal can be obtained, motor-evoked potentials and/or somatosensory-evoked potentials can be used to detect neurological injury during neuromuscular scoliosis surgery
Postoperative considerations
Admit to HDU/ICU postoperatively
Care needs to be taken with regards the titration of analgesia so that pain relief is adequate and sedation is minimized to ensure respiratory effort is not compromised. Postoperative analgesia must be closely monitored by a specialist pediatric pain team with 24-hr cover or intensive care specialists
Frequent and aggressive chest physiotherapy should be used. Non-invasive positive airway pressure support may be required postextubation (*e.g.,* BIPAP)
A clear management plan should be constructed when the patent is transferred back to the ward
Seek expert advice to optimize nutritional status
Consult parents or caregivers to help assess the child postoperatively
Mobility postoperatively:
Log roll for bed mobility
Sitting on edge of bed day one postoperative
Transfer to chair postoperative day 2
Walking (if possible) postoperative day 3
Postoperative reviews should be carried out at:
6 wk
Then every 2–3 mo over the first yr
Annually thereafter
The following should be used to assess surgical outcome: complications including bleeding, infection and duration of ICU stay; Cobb angle and achievement of fusion; respiratory status; sitting balance, function and quality of life; parent and carer satisfaction

incorporate a comprehensive approach to multiple aspects of health in subjects with Rett syndrome and scoliosis. This document can be used as a plan to support clinicians with less experience of Rett syndrome, to promote discussion among clinicians and caregivers, and act as a catalyst for further research.

■ Key Points

- A set of clinical guidelines for the management of scoliosis in Rett syndrome were developed based on clinician expertise and clinical evidence.
- Specific features of Rett syndrome such as genotype, seizures, gastrointestinal disturbances, and osteoporosis impact on the management of scoliosis.
- A life-span approach commencing before the development of scoliosis and including comprehensive management from medical, therapy, and surgical specialists is described.
- Spinal fusion is recommended when the Cobb angle is approximately 40° to 50°.

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