Airway management in infants with Robin sequence in the United Kingdom and Ireland: a prospective population-based study

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Abstract

Abstract Objective There is currently no consensus about managing upper airway obstruction (UAO) in infants with Robin sequence (RS), in terms of treatment efficacy or clinical outcomes. This study describes UAO management in UK/Ireland, and explores relationships between patient characteristics, UAO management, and clinical outcomes in the first two years of life. Methods Active surveillance of RS throughout UK/Ireland via the British Paediatric Surveillance Unit and nationally commissioned cleft services. Clinical data were collected at initial notification and 12-month follow-up. Results 173 infants with RS were identified, of which 47% had additional congenital anomalies or an underlying syndrome (non-isolated RS). Two-thirds (n=119) required an airway intervention other than prone positioning: non-surgical in 84% and surgical (tracheostomy) in 16%. Nasopharyngeal airway (NPA) was the most common intervention, used in 83% (n=99) for median 90 days (IQR 136). Surgical UAO management was associated with prolonged hospital admission, higher prevalence of neurodevelopmental delay (NDD), lower weight-for-age z-scores, and delayed oral feeding. These findings were not attributable to a higher prevalence of non-isolated RS in this group. Although more commonly associated with non-isolated RS, growth faltering was also identified in 48%, and NDD in 18%, of isolated RS cases. Conclusions In UK/Ireland, most infants with RS are managed with NPA and tracheostomy is reserved for refractory severe UAO. Clinical outcomes and duration of use indicate that NPA is a safe and feasible first-line approach to UAO. Longitudinal assessment of neurodevelopment and growth is imperative, including in children with isolated RS. Current variations in practice reinforce the need for evidence-based treatment guidelines.

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Objective

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Methods
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Surgical UAO management was associated with prolonged hospital admission, higher prevalence of neurodevelopmental delay (NDD), lower weight-for-age z-scores, and delayed oral feeding. These findings were not attributable to a higher prevalence of non-isolated RS in this group. Although more commonly associated with non-isolated RS, growth faltering was also identified in 48%, and NDD in 18%, of isolated RS cases.

Conclusions
In UK/Ireland, most infants with RS are managed with NPA and tracheostomy is reserved for refractory severe UAO. Clinical outcomes and duration of use indicate that NPA is a safe and feasible first-line approach to UAO. Longitudinal assessment of neurodevelopment and growth is imperative, including in children with isolated RS.

Current variations in practice reinforce the need for evidence-based treatment guidelines.

Abbreviations
AOR Adjusted odds ratio
CPAP Continuous positive airway pressure support
ETT Endotracheal tube
GDD Global developmental delay
IQR Interquartile range
LOS Length of stay
MDO Mandibular distraction osteogenesis
NDD Neurodevelopmental delay
NPA Nasopharyngeal airway
OR Odds ratio
RS Robin sequence
UAO Upper airway obstruction
UK United Kingdom

Introduction
Robin sequence (RS) is a congenital disorder characterized by micrognathia and glossoptosis, resulting in upper airway obstruction (UAO). Cleft palate is a common additional feature. In approximately half of cases, RS is part of a wider genetic syndrome or associated with additional congenital abnormalities (non-isolated RS), which may result in a more severe disease phenotype with worsened clinical outcomes. UAO
is a clinically important component of RS which can result in substantial morbidity including growth faltering and prolonged hospital admission\textsuperscript{5-7}. Additional potential consequences of untreated UAO in children include neurocognitive impairment, behavioral problems, and cardiac dysfunction \textsuperscript{8, 9}. Diagnosing UAO can be challenging in infants with RS, as initial presentation may be subtle with minimal and intermittent signs of respiratory distress\textsuperscript{10}. Where UAO is missed based on early clinical assessment, it may not be recognized until several weeks after birth when infants present with feeding problems or suboptimal growth \textsuperscript{6}.

In clinical practice, various interventions can be used for management of UAO including a conservative approach with prone positioning during sleep, non-surgical management such as nasopharyngeal airway (NPA) insertion, and surgical interventions including mandibular distraction osteogenesis (MDO) and tracheostomy insertion. There is currently no consensus about best practice due to a lack of studies comparing clinical outcomes, and approaches consequently differ between treatment centers and countries \textsuperscript{11}.

The primary aim of this study was to describe the management of RS-associated UAO in the United Kingdom and Ireland (UK/Ireland) and ascertain whether there are differences in clinical outcomes, including growth and neurodevelopment, in the first two years of life according to UAO management approach. Our secondary aims were to determine whether there is geographical variability in outcomes, potentially reflecting the impact of different practices between treatment centers, and whether outcomes differed between children with isolated and non-isolated RS.

**Methods**

We conducted a surveillance study through the British Paediatric Surveillance Unit (BPSU), an active surveillance system for childhood rare diseases that involves case reporting by consultant paediatricians and neonatologists across UK/Ireland. Cases were concurrently reported by nationally commissioned regional cleft services.

The surveillance case definition of RS applied included live-born infants with each of the following clinical features: (1) cleft palate, (2) glossoptosis or micro/retrognathia, (3) evidence of resulting clinical compromise (UAO or growth faltering or feeding difficulties). This definition was developed collaboratively by the study authors and BPSU scientific committee as, at the time of study onset, there was no consensus definition for RS (an international consensus definition by Breugem and colleagues has since been published \textsuperscript{1}). When developing the definition, we considered that UAO can be intermittent in early infancy and some babies with undiagnosed UAO may present with growth faltering, hence including infants with either of these clinical features rather than mandating the presence of UAO. Furthermore, we predicted that thresholds for sleep studies and airway intervention would vary between centres, meaning that diagnosis of UAO may be inconsistent across the study population. For further discussion around the case definition, and a comprehensive description of the study methods including how cases were designated as isolated or non-isolated RS, refer to the previous publication from this patient cohort\textsuperscript{12}.

**Data collection**

Reporting clinicians completed two surveys a minimum of 12 months apart. Data collected included details of UAO management, use of sleep studies, and the following clinical outcomes: initial hospital length of stay (LOS), method and duration of feeding support, growth trajectory, status and timing of cleft palate repair, and results of neurodevelopmental assessments.

Growth faltering was defined according to National Institute for Health and Care Excellence diagnostic criteria based on UK-WHO growth standards\textsuperscript{13}, and was calculated from a minimum of two weight measurements recorded at the following timepoints: birth, last recorded weight on initial survey, cleft palate repair, and last recorded weight on follow-up survey. Duplicate weight measurements were removed, and serial weights were then placed in chronological order labelled W0 (earliest measurement) to W3 (most recent measurement). We defined growth faltering as early if it occurred within the first 3 months of life and late if it occurred beyond this time point.

Neurodevelopmental delay (NDD) was defined as a delay in one, and global developmental delay (GDD)
defined as a delay in two or more, developmental domains based on the reporting clinician’s assessment of developmental milestone attainment.

**Statistical analysis**

Summary statistics were used, including median and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were compared using Chi-squared or Fisher’s exact tests, and continuous variables using Wilcoxon-Mann-Whitney U or Kruskal-Wallis tests. Weight-for-age z-scores and percentiles were calculated using the R library childsds. Logistic regression models were fitted to estimate risk factors for binary outcomes. Spline models, with a child-based random effect term in the intercept and allowing for possible interactions, modelled age trajectories of weight for age z-scores. Pairwise deletion of missing data was applied. Statistical significance was set at the 0.05 level. Analyses were performed in the R language and environment for statistical computing version 4.0.5 and SPSS version 27.0 or later (IBM Corp., Armonk, NY).

**Ethics**

This study was approved by the South-East Scotland Research Ethics Committee (15/SS/0049) and supported by the Health Research Authority Confidentiality Advisory Group (15/CAG/0141) to collect data without patient consent.

**Results**

During the surveillance period, 173 cases of RS meeting the case definition were identified. Median age at follow-up was 2.0 years (IQR 1.3 [1.5-2.7] years). A full description of the clinical characteristics of this cohort has been published. 47% (n =81) had non-isolated RS, of which the most common genetic diagnoses were Stickler syndrome (n =20; 12% of RS cases) and chromosomal abnormalities (n =17; 10% of RS cases).

Sixty-nine percent of children (n =119) required an intervention other than positioning during sleep. 84% (n =100/119) were managed with a non-surgical intervention. The types of airway intervention used are summarized in Figure 1. NPA was the most common intervention, used in 83% of cases (n =99/119). Median age at NPA insertion was 5 days (IQR 14 [1-15] days) and duration of use was 90 days (IQR 136 [19-155] days). One-third of infants with RS (32%; n =56) were discharged home with NPA in place.

Continuous positive airway pressure support (CPAP) and ventilation via an endotracheal tube (ETT) were used in 28% and 14% of infants, respectively. Both were short-term interventions: CPAP was used for a median of 3 days (IQR 63 [1-64] days) and ETT for median 7 days (IQR 13 [3-16] days). Eleven children used CPAP at home; within this group, CPAP was started at a median age of 153 days (IQR 113 [139-252] days). Three children were still using CPAP at last follow-up, at a median age of 2.1 years (8 months – 3 years). Among the other eight, CPAP was used for a median of 191 days (IQR 241 [65-306] days).

11% of RS infants (n =19) underwent tracheostomy insertion, with two children subsequently undergoing MDO surgery. Median age at tracheostomy was 33 days (IQR 49 [18-67] days). Non-surgical airway interventions (CPAP, NPA, etc.) frequently preceded tracheostomy insertion with a median of two interventions per child. The need for airway intervention other than positioning was not related to birth weight (p= 0.559), gestational age (p= 0.749) or having non-isolated RS (odds ratio (OR) 1.8 [95% CI 0.9-3.5], p=0.074). In a logistic regression model, prior ETT use was the only independent predictor of the need for surgical airway intervention (adjusted odds ratio (AOR) 5.08 [95% CI 1.5-17.7]; p =0.011) (Table 1).

Although the proportion of children managed with an airway intervention (p =0.002) and discharged from hospital with NPA (p =0.007) differed significantly between countries, use of surgical airway interventions was similar (Supplementary Table 1).

Sleep diagnostics to inform airway management were carried out in 72% (n =121/167) of children, with median age of 22 days (IQR 64 [9-73] days) at first study. Of the 351 studies performed, the most common study types were oximetry (52%, n =183) and cardiorespiratory polygraphy (25%, n =88). Polysomnography accounted for only 4% (n =15) of studies (Supplementary Figure 1).
Clinical outcomes

Clinical outcomes are summarized in Table 2, and a comparison of outcomes between countries is summarized in Supplementary Table 2.

Hospital length of stay in the neonatal period

Of the 160 infants admitted to hospital in the neonatal period, information about hospital LOS was available for 96% (n =153). Median duration of initial hospital admission was 21 days (IQR 28 [12-40] days). LOS was shorter in cases where no airway intervention was required (median 12 days, IQR 16 [5-21] days) compared to when non-surgical (median 26 days, IQR 23 [17-40] days) or surgical (median 60 days, IQR 98 [31-129] days) interventions were used (p <0.001).

Neurodevelopment

NDD was reported in 33% of infants (n =45/138) based on clinician assessment. Only four children underwent formal neurodevelopmental testing. Of the 45 infants with NDD, 64% (n =29/45) had GDD, and 36% (n =16/45) had a specific delay, most commonly affecting speech and language development (n =9). One-third of infants with speech delay had a tracheostomy.

There was no difference in NDD prevalence between children who received and did not receive an airway intervention other than positioning. However, children who underwent surgical airway management were significantly more likely to have NDD (OR 2.93 [95% CI 1.10-7.75], p =0.048) compared to children who did not undergo airway surgery.

Growth and feeding support

Ninety-four percent of children (n =159/170) received supplemental nasogastric tube feeding in infancy, and 10% (n =17) ultimately underwent gastrostomy insertion. Of the 80% of children (n =128/160) who had established full oral feeding at last follow-up, median age at discontinuing tube feeds was four months (118 days, IQR 30 – 121 days).

Across the group, median weight-for-age z -scores declined in the first 2-3 months of life (-0.19 at birth to -0.95 at median age 73 days; mean difference -0.73 z -scores) with gradual recovery by the end of the follow-up period (Supplementary Table 3). Children managed with a surgical airway had lower median weight-for-age z -scores at all time points than those managed non-surgically or without an airway intervention. Although surgical intervention was associated with slightly improved growth trajectory in the initial postnatal period, this was not sustained and there was no evidence of significant catch-up growth (Supplementary Table 4 and Supplementary Figure 2).

Growth faltering was present in 58% of infants (n =95/164) and was more common in those who required an airway intervention other than positioning (OR 2.35 [95% CI 1.18-4.69], p =0.014). No difference in prevalence was seen between infants managed with surgical or non-surgical interventions. Children managed with a surgical airway had a higher prevalence of surgical tube feeding (OR 5.87 [95% CI 1.87-18.47] p =0.005) and were less likely to be orally fed at follow-up (OR 0.09 [95% CI 0.03-0.29], p <0.001) compared to those managed without a surgical airway.

Mortality

Seven infants (4%) died during follow-up, at a median age of 43 days (IQR 80 [16-96] days). All had non-isolated RS (chromosomal disorder, n =5; Sotos syndrome and Smith-Lemli-Opitz syndrome, n =1). The cause of death was given in five cases: respiratory (n =2), multi-organ failure, sudden infant death syndrome, necrotizing enterocolitis (n =1). Six children had required airway intervention and three had a tracheostomy. Deaths were significantly more common among children who underwent surgical airway management than in children managed non-surgically or without an airway intervention (OR 7.031 [95% CI 1.44-34.25], p =0.030).
On logistic regression analysis adjusting for presence of non-isolated RS, preterm birth, and country of birth, surgical airway intervention was an independent predictor of NDD, surgical feeding tube insertion, and lower probability of establishing full oral feeding by last follow-up (Table 3).

Outcomes by RS classification

Children with non-isolated RS had a higher prevalence of growth faltering, NDD, and surgical tube feeding, higher mortality rate, and longer hospital LOS and duration of feeding support compared to children with isolated RS (Table 4). Apart from hospital LOS, each of these associations remained statistically significant in a regression model adjusting for preterm birth and country of birth (Supplementary Table 5). There was a non-significant trend toward a higher probability of surgical airway intervention in infants with non-isolated RS (OR 2.71 [95% CI 0.98-7.50], \( p = 0.048 \)).

Compared to children with other forms of non-isolated RS, children with Stickler syndrome had a lower prevalence of NDD (\( p =0.002 \)) and were more likely to have established full oral feeding by follow-up (\( p <0.001 \)). No child with Stickler syndrome was managed with surgical airway or feeding interventions, or died during the follow-up period.

Discussion

This birth cohort study of infants with RS in UK/Ireland identified a high frequency of UAO requiring airway intervention other than positioning, with NPA the most-used treatment modality. Children with NPA were frequently managed at home and treatment could typically be discontinued by 3-6 months of age. Surgical airway management was reserved for cases of severe UAO, usually after several other methods of non-surgical airway support had been attempted. Children who underwent surgical airway intervention were noted to have a higher probability of NDD and surgical feeding tube insertion, and a lower probability of having established full oral feeding by last follow-up. This association remained statistically significant after adjustment for potential confounding factors including presence of non-isolated RS. Furthermore, hospital LOS in the neonatal period was significantly longer for children who underwent surgical airway management than those managed with more conservative measures. Our findings support the previously reported use of non-surgical interventions as first-line management for UAO in RS\(^{17-19}\) and further demonstrate that UAO is generally a self-limiting process that improves over the first year of life\(^{20-22}\).

Studies from several pediatric treatment centres in the UK have previously reported frequent use of NPA\(^ {10, 17, 23}\) and this study confirms this approach as the first-line intervention for UAO management throughout UK/Ireland. This contrasts with the treatment approach taken in some other countries. A German surveillance study of RS reported that orthodontic therapies (feeding plate or pre-epiglottic baton plate) were used in three-quarters of infants, compared to CPAP in 35% and NPA in 21% of cases\(^ {5}\). CPAP has alternatively been described as the non-surgical intervention of choice in some French and Australian centers\(^{11, 24, 25}\). Studies from the USA indicate a lower threshold for surgical intervention, with MDO being the first-line procedure\(^ {4, 26}\). For example, 64% of RS infants in Cincinnati, Ohio underwent airway surgery over a 14-year period\(^ {27}\).

Within UK/Ireland we did observe some geographical differences in management practices, including duration of hospital admission, age at cleft palate repair, threshold for performing sleep studies and frequency of NPA use. This may reflect variations in multidisciplinary team working between cleft and paediatric respiratory teams, as well as a lack of multi-centre long term outcome studies to inform best practice.

Growth

We identified growth faltering in 60% of infants with RS during the first two years of life, despite 94% receiving supplementary tube feeds for a median duration of 4 months. Growth faltering in RS is complex and likely multifactorial. Affected infants, particularly those with clefts, have abnormal sucking and swallowing mechanics which can result in prolonged feeding time and increased energy expenditure\(^ {28}\). Chronic UAO is also likely contributory, and growth faltering has been proposed as an indicator of subclinical obstruction based on observed improvement in weight gain after introduction of airway interventions including...
pre-epiglottic baton plate and NPA. Indeed, we used this as part of our definition for RS. However, our finding that growth faltering was more common in infants who received an airway intervention than those without active airway management, with highest rates among children with definitive alleviation of UAO by tracheostomy insertion, implies that subclinical UAO leading to growth faltering was not a major contributory factor in our cohort. Similarly, our finding of consistently lower weight-for-age z-scores in children managed with a surgical airway intervention indicates that surgical management did not optimize growth by treating UAO more definitively than non-surgical methods. This finding contrasts with studies reporting that weight gain in RS infants in the first two years of life is not influenced by UAO severity, or the type of airway intervention used. This discrepancy may relate to differences between studies in terms of the types of surgical and non-surgical interventions used, and follow-up durations.

A further risk factor for growth faltering in our cohort was non-isolated RS, which has also been reported within other RS cohorts, and may reflect reduced growth potential in children with RS-associated syndromes.

Neurodevelopmental delay

In this population, NDD was reported in one-third of cases and was significantly more common in children with non-isolated RS, which is consistent with existing published research. However, even among children with isolated RS, NDD was identified in 18% and GDD in 7% of cases. This is substantially higher than the estimated population prevalence of NDD (3-4%) and GDD (1-3%) in the UK.

There are conflicting reports about whether children with isolated RS are at risk of NDD. Several studies have reported neurocognitive impairment, which is typically mild and demonstrates improvement over time. However, case-control studies involving Denver II developmental screening and intelligence quotient testing have reported similar results between children with RS and age-matched healthy controls.

Children with isolated RS may be at risk of adverse neurodevelopmental outcomes for several reasons. Cleft palate is a risk factor for velopharyngeal and Eustachian tube dysfunction, which can adversely affect speech production and cause conductive hearing loss, resulting in early language delay. Protracted hospital admissions in early childhood, as are often endured by infants with RS, are a further recognized risk factor for NDD. Additionally, uncontrolled sleep-disordered breathing leading to oxygen desaturation, arousals, and sleep fragmentation is a known risk factor for cognitive and behavioral problems. In our cohort, NDD was significantly associated with surgical airway intervention despite adjusting for the presence of non-isolated RS, which may reflect the impact of a protracted hospital admission or early severe UAO on neurodevelopment. This contrasts with the findings of Thouvenin and colleagues, who found no difference in neurodevelopmental outcomes between infants with RS who were managed with and without tracheostomy over a follow-up period of up to 12 years.

It is possible that the high prevalence of NDD among infants with isolated RS in our cohort may reflect underdiagnosis of non-isolated RS; given the strong association between non-isolated RS and NDD, we would advocate thorough assessment for a possible genetic diagnosis in cases of apparent isolated RS with significant and persistent NDD.

Outcomes according to RS genetic classification

In our cohort, 53% of infants had isolated RS. This concurs with a literature review by Gomez-Ospina, which identified isolated RS in 50% of 1,385 RS cases from 16 published studies. Stickler syndrome was the most common RS-associated genetic diagnosis, as is consistently reported by population-based studies from a range of countries.

Non-isolated RS is reported to have a more clinically severe phenotype than isolated RS across various characteristics and outcome measures including severity of UAO, need for surgical airway and feeding support, NDD, and survival. In our cohort, non-isolated RS was associated with many of these adverse outcomes but was not predictive of the need for airway support. Similarly, the probability of surgical
airway intervention was not significantly increased in children with non-isolated RS when we adjusted for other differences between the two groups.

We found that RS associated with Stickler syndrome had a less severe clinical phenotype than other forms of non-isolated RS, including a significantly lower probability of needing surgical airway or feeding support, and a lower prevalence of NDD. It might therefore be appropriate for healthcare providers to regard RS associated with Stickler syndrome as a separate entity to non-isolated RS when considering management and prognosis.

**Strengths**

This study utilized active surveillance based on well established, standardized national reporting methodology, and achieved high reporting card (94%) and survey (85%) response rates. Additionally, we used dual reporting based on data submitted by each of the nationally designated Cleft Units across UK/Ireland. Cleft care is delivered only within nationally commissioned units, so any baby with cleft palate associated with RS would be known to one of these units. Therefore we are confident that we have achieved high case ascertainment for RS with cleft palate. This contrasts with previous population-based studies of RS, which may have missed children with RS who did not require hospital admission or who may have been treated in smaller or private hospitals. We applied a broad case definition, accepting growth faltering or feeding difficulties as surrogate markers of overt UAO and evidence of clinical compromise, given that UAO may be missed on initial assessment and potentially remain undiagnosed until several weeks of age. This study can therefore be seen to represent the full spectrum of severity of respiratory involvement in RS.

By collecting data at two time points we were able to validate information submitted in the initial survey and observe the clinical trajectory of affected children over time. Furthermore, this approach enabled more accurate identification of non-isolated RS and associated syndromes as this information may not be apparent in early infancy and requires subsequent re-evaluation. Finally, the study’s prospective design minimizes risk of recall bias.

**Limitations**

Data were collected from existing routine medical records by reporting clinicians, and patients were not recalled for clinical assessment. This resulted in instances of missing data and may also affect the validity of some study findings. For example, identification of non-isolated RS was based on available information about clinical features and genetic evaluation results. As clinical geneticist evaluation and/or formal genetic testing were determined by individual centers’ protocols rather than by a standardized approach to genetic assessment, this may have resulted in underestimation of non-isolated RS and under-diagnosis of specific syndromes.

Similarly, as sleep studies were not carried out in every case, there may be underestimation of sleep disordered breathing requiring intervention in this cohort. However, a high prevalence of undertreated UAO seems unlikely given that the best growth trajectories were seen in children who were managed without an airway intervention.

We did not include cases of RS without cleft palate in this study. However, as UAO severity and intervention rates are reported to be comparable in cases of RS with and without cleft palate, exclusion of non-cleft RS cases is unlikely to have significantly impacted our findings. It is conceivable that the prevalence of NDD, particularly speech delay, and the need for feeding support may be higher in cases of RS with associated cleft and this should be borne in mind when generalizing the results of our study to the wider RS population.

Although we tried to adjust to differences between comparison groups using regression analysis, there may be additional confounding factors that we were unable to measure with this study. For example, social factors including proximity of the child’s home to the admitting hospital may have impacted hospital LOS in the neonatal period.

Finally, in contrast to other countries where MDO is a commonly used surgical intervention, tran-
cheostomy was the prevailing surgical intervention for RS-related UAO in UK/Ireland, which may make our study findings less generalizable to other populations.

To summarize, this active surveillance study of RS in UK/Ireland, with high case ascertainment, found that two-thirds of infants with RS required airway intervention. NPA is the most commonly used intervention throughout this population, with surgery reserved for cases of refractory severe UAO. In contrast to some international RS treatment centers, tracheostomy is favoured over MDO in UK/Ireland. Children managed with surgical airway interventions had a higher prevalence of NDD, prolonged hospital admission, and delayed oral feeding, which were not attributable to the higher prevalence of non-isolated RS in this group. Furthermore, surgery was not protective against growth faltering compared to non-surgical treatment methods.

Within this large population-based RS cohort, in which genetic evaluation was commonly used to delineate RS genetic classification, there was a high prevalence of NDD and growth faltering. Although both were more common in infants with non-isolated RS, they were also present in cases of isolated RS. Further research is needed better understand the cause of these morbidities in children with isolated RS, and longitudinal assessment of neurodevelopment and growth is imperative in this at-risk patient group.

Conclusions

There are variations in the approach to diagnosis, follow-up and management of UAO in children with RS within UK/Ireland, with further variation reported internationally. Standardization of data collection across centres is essential to evaluate effectiveness of treatment protocols, inform evidence-based guidelines, and ensure that decisions are based on objective assessment of clinical severity rather than individual treatment center conventions and resource availability. International, multicentre studies or RS patient registries would allow comparison of surgical and non-surgical interventions, alongside longitudinal assessments of neurodevelopment and growth, and enable treatment recommendations to be optimized.

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