

## Rigid Spine Syndrome among Children in Oman

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### متلازمة تصلب العمود الفقري لدى الأطفال في سلطنة عمان

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**ABSTRACT: Objectives:** Rigidity of the spine is common in adults but is rarely observed in children. The aim of this study was to report on rigid spine syndrome (RSS) among children in Oman. **Methods:** Data on children diagnosed with RSS were collected consecutively at presentation between 1996 and 2014 at the Sultan Qaboos University Hospital (SQUH) in Muscat, Oman. A diagnosis of RSS was based on the patient's history, clinical examination, biochemical investigations, electrophysiological findings, neuro-imaging and muscle biopsy. Atrophy of the paraspinal muscles, particularly the erector *spinae*, was the diagnostic feature; this was noted using magnetic resonance imaging of the spine. Children with disease onset in the paraspinal muscles were labelled as having primary RSS or rigid spinal muscular dystrophy. Secondary RSS was classified as RSS due to the late involvement of other muscle diseases. **Results:** Over the 18-year period, 12 children were included in the study, with a male-to-female ratio of 9:3. A total of 10 children were found to have primary RSS or rigid spinal muscular dystrophy syndrome while two had secondary RSS. Onset of the disease ranged from birth to 18 months of age. A family history was noted, with two siblings from one family and three siblings from another (n = 5). On examination, children with primary RSS had typical features of severe spine rigidity at onset, with the rest of the neurological examination being normal. **Conclusion:** RSS is a rare disease with only 12 reported cases found at SQUH during the study period. Cases of primary RSS should be differentiated from the secondary type.

**Keywords:** Rigid Spine Syndrome; Rigid Spine Muscular Dystrophy; Selenoprotein; Children; Magnetic Resonance Imaging; Oman.

**المخلص: الهدف:** تصلب العمود الفقري مرض شائع لدى الكبار ولكنه نادر الحدوث عند الأطفال. الهدف من هذه الدراسة هو اكتشاف حالات تصلب العمود الفقري لدى الأطفال العمانيين. **الطريقة:** تم استخراج المعلومات عن الأطفال الذين تم تشخيصهم بمتلازمة تصلب العمود الفقري في الفترة بين 1996 و 2014 في مستشفى جامعة السلطان قابوس بمسقط، سلطنة عمان. تم تشخيص متلازمة تصلب العمود الفقري اعتماداً على التاريخ المرضي، والفحص السريري، والفحوصات الألكتروفسيولوجية، وصور الأشعة و تحليل عينة من العضلة. ما يميز هذه المتلازمة هو وجود ضمور في العضلة المحيطة بالنخاع بالتحديد وهو ما يمكن تشخيصه عن طريق أشعة الرنين المغناطيسي للعمود الفقري. وصفت إصابات الأطفال بأولية أو ثانوية بناءً على العضلة المصابة أولاً. **النتائج:** خلال فترة 18 سنة، تم تشخيص 12 طفلاً بمتلازمة تصلب العمود الفقري، بنسبة الذكور إلى الإناث 9 إلى 3. تم تشخيص متلازمة تصلب العمود الفقري الأولي في 10 من الأطفال أما الاثنان المتبقيان فتم تشخيصهم بمتلازمة تصلب العمود الفقري الثانوي. تم ملاحظة أن أعراض المرض تبدأ عادة في الفترة ما بين الولادة وحتى عمر 18 شهراً. كان هناك تاريخ عائلي للمرض في حالتين من الأطفال المصابين. الفحص السريري أوضح أن الأطفال المصابين بمتلازمة تصلب العمود الفقري الأولي لديهم تصلب شديد في عضلات العمود الفقري. أما بقية فحوصات الأعصاب السريرية فكانت سليمة. **الخلاصة:** متلازمة تصلب العمود الفقري مرض نادر الحدوث، وقد تم تسجيل 12 حالة فقط في مستشفى جامعة السلطان قابوس خلال فترة الدراسة.

**الكلمات المفتاحية:** متلازمة تصلب العمود الفقري؛ تصلب العمود الفقري الحثلي؛ سلينوبروتين؛ الأطفال؛ أشعة الرنين المغناطيسي؛ عمان.

#### ADVANCES IN KNOWLEDGE

- Rigid spine syndrome (RSS) is common in adults but is infrequently seen among children. This study presents a large series of paediatric patients with this rare condition in Oman.

#### APPLICATION TO PATIENT CARE

- The results of this study support the implementation of support groups and family counselling services for the parents and guardians of children suffering from RSS in Oman.
- Genetic tests were available for only three patients during the study period. The development of genetic testing facilities in Oman is recommended for diagnosing this condition among those with a family history of RSS.
- Paediatricians and physicians should learn to recognise this rare entity, particularly as diagnosed RSS patients will require multidisciplinary care.

**R**IGIDITY OR STIFFNESS OF THE SPINE IS common in adults and among the elderly but is rarely seen in children.<sup>1,2</sup> In adults, the disease mainly results in a bent spine (forward bending), often with a bent or drooping head. In children, while the spine may also be bent, the head remains upright and the neck becomes so stiff that the child cannot look to the ground. Differences have been noted between the underlying aetiopathology of a rigid spine in children and adults, although the usual causes are bone, neuromuscular and brain disorders.<sup>3,4</sup> Inheritance patterns also differ between adults and children as the condition is generally autosomal dominant in the former and recessive in the latter.<sup>5</sup> The disease presents between the 4–6<sup>th</sup> decade of life for adults and during the first decade for children.<sup>5</sup> For adults, this condition is known as axial myopathy, *camptocormia*, rigid spine syndrome (RSS) and, more recently, paraspinal neuromuscular syndrome.<sup>4,6,7</sup>

Rigidity of the spine is noted in the late stages of several childhood muscular dystrophies and myopathies. In these diseases, the rigid spine is due to the spread of the disease to the muscles and the late involvement of the paraspinal muscles.<sup>5</sup> This is known as secondary RSS; a specific muscle disease is usually the underlying cause. Rigid spinal muscular dystrophy syndrome (primary RSS) develops when the onset of the disease occurs in the paraspinal muscles and then spreads to the other muscles of the body.<sup>5,8</sup> In the primary form of RSS, the muscle disease is often of non-specific origin or is due to congenital myopathies such as multicore disease or desmin-related myopathy with Mallory body-like inclusions. In these cases, the disease originates outside the dystrophin, glycoprotein or extracellular matrix.<sup>9</sup> The muscle histopathology is therefore non-specific as the myopathy changes with fibro-fatty accumulation.<sup>10–12</sup> The diagnosis of RSS is based on the clinical course of the illness as well as biochemical, electrophysiological, histopathological, genetic and radiological findings.

In cases of primary RSS, a magnetic resonance imaging (MRI) scan of the spine will reveal atrophy of the paraspinal muscles, particularly the erector *spinae*.<sup>13</sup> Selenoprotein dysfunction has been recognised as the main defect in the muscles of children with primary RSS; mutations in the *selenoprotein N1 (SEPN1)* gene-related myopathy were found to be associated with this disease and primary RSS was mapped to the 1p35–36 chromosome in four siblings.<sup>9,13</sup> This study aimed to report on the characteristics of RSS among children in Oman.

## Methods

Children diagnosed with RSS were enrolled in the study consecutively at presentation between 1996 and 2014 at the Sultan Qaboos University Hospital (SQUH) in Muscat, Oman. After their initial presentation, the children were followed over the study period. Children were suspected of having RSS if there was restricted neck movement and bending of the spine.

A diagnosis of RSS was based on the following clinical features: an inability to look down due to limited neck movement; restriction of overall spine mobility and normal limb strength which did not affect day-to-day activities; no difficulty in swallowing, breathing or speaking; and no bone or joint involvement. Results from biochemical tests, imaging and muscle biopsies, as well as electrophysiological findings, were also used to make a diagnosis. Genetic tests were available for only three patients during the study period. These children did not have features of other dystrophinopathies so associated tests were not performed.

Formal consent for inclusion in this study was obtained from the parents or guardians of the children. This study was approved by the Medical Research & Ethics Committee at the College of Medicine & Health Sciences of Sultan Qaboos University (MREC#675).

## Results

A total of 12 children with RSS presented to SQUH over the 18-year study period. Seven of these children had been previously reported in a case series.<sup>5</sup> The estimated prevalence of RSS in Oman was therefore one per 170,000 of the general population or six per one million, based on a national population of approximately two million.<sup>14</sup> There were nine male and three female patients. Onset of the disease ranged from birth to 18 months old (mean age: eight months and five days), although the parents of one child could not remember the exact time of disease onset. Seven of the children (58.3%) had delayed gross motor skill development; the remaining five patients (41.7%) had normal milestones. A family history was noted, with two siblings from one family and three siblings from another (n = 5). The remainder of the patient group were single cases (n = 7).

A total of 10 children were found to have primary RSS (83.3%) while the remaining two had the secondary form of the disease (16.7%). Muscle biopsies were performed in 41.7% of the children

**Table 1:** Clinical, laboratory and imaging features of children diagnosed with rigid spine syndrome (N = 12)

Disease type	Age at onset in months	Development	Age at presentation in years	Creatine kinase level* in IU/L	EMG	ECG	Muscle biopsy findings	Spine MRI findings
Primary	6	N	12	94	Myo	Normal	Myo, fat and collagen	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary	6	N	Not seen	Not performed	Not performed	Not performed	Not performed	Not performed
Primary	Unknown	N	7	150	Myo	Normal	None	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary	18	N	5	145	Myo	Normal	None	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary	8	N	5	151	Myo	Normal	Patient did not consent	Muscle wasting, hypointensity and fibro-fatty infiltration
Secondary <sup>†</sup>	10	Motor delay	2	856	Myo	Normal	Mitochondrial changes in shape and size	Normal
Primary <sup>‡</sup>	5	Motor delay	6	147	Myo	Normal	Non-specific Myo	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary	12	Motor delay	11	200	Myo	Normal	Patient did not consent	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary	15	Motor delay	9	187	Myo	Normal	Patient did not consent	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary	15	Motor delay	8	230	Myo	Normal	Patient did not consent	Muscle wasting, hypointensity and fibro-fatty infiltration
Primary <sup>†</sup>	6	Motor delay	10.4	123	Myo	Normal	Multicore disease	Not performed
Secondary	At birth	Motor delay	5.6	800	Myo	Normal	Congenital Myo of uncertain type	Not performed

EMG = electromyography; ECG = echocardiography; MRI = magnetic resonance imaging; Myo = myopathy.

\*Normal range: 62–302 IU/L. <sup>†</sup>Genetically confirmed. <sup>‡</sup>Genetically negative.

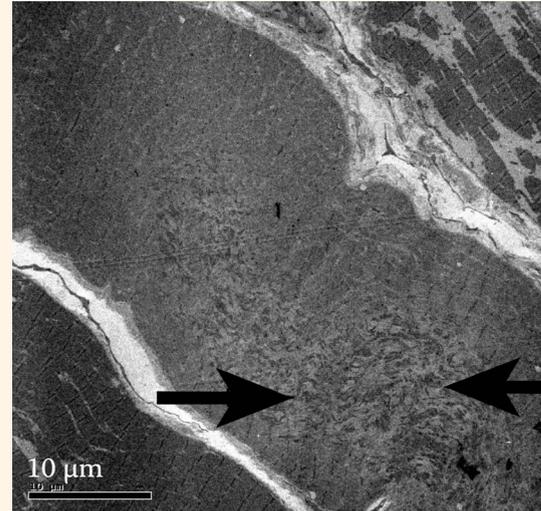
(three patients with primary RSS and two with secondary RSS). Histopathological findings were available for five patients (three with primary RSS and two with secondary RSS) and genetic information was available for two children with primary RSS and one with secondary RSS. One child with primary RSS

was previously diagnosed with stiff person syndrome. A summary of the clinical and imaging features of all patients is available in Table 1.

On examination, the children with primary RSS had typical features of severe spine rigidity although their other neurological findings were normal. Gowers'



**Figure 1:** Photograph of a child diagnosed with primary rigid spine syndrome showing wasted neck muscles and an inability to bend the neck. Respiratory difficulties required him to be on nasal oxygen supplementation.



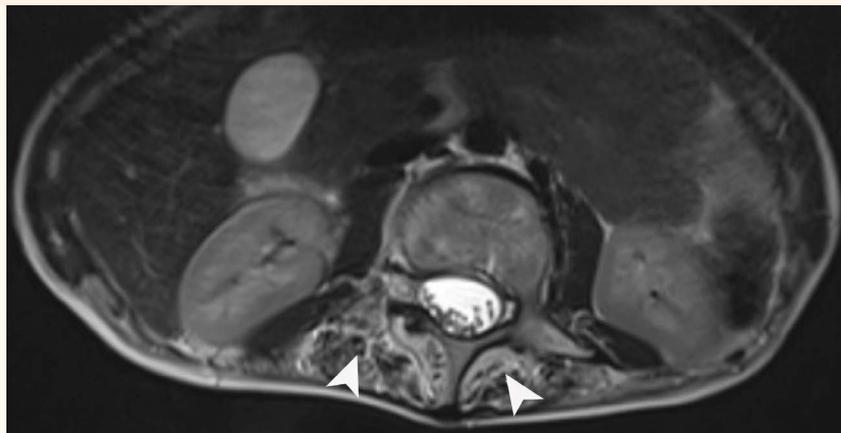
**Figure 2:** Electron microscopy showing multicore bodies in the muscle (arrows). This confirmed the diagnosis of primary rigid spine syndrome.

sign was negative in all 10 of these children. MRI scans of the spine were diagnostic in cases of primary RSS. These scans revealed typical features of muscle mass loss in the paraspinal muscles and low signals of fibrofatty infiltration were seen replacing the muscle tissue. Two children with primary RSS had non-specific myopathy while a third child had a multicore type of congenital myopathy. The following case may serve as a representative example of primary RSS observed in this study.

A 10-year-old boy with breathing difficulties and repeated chest infections was referred to SQUH from a peripheral hospital. Initial signs of the disease began in the first year of life with motor developmental delay; his parents noted that, compared to his siblings, the child was slower in learning to sit. However, he was able to walk by the time he was two years old and all social and mental milestones were achieved in an appropriate timeframe compared to his siblings. After the age of six years, the child contracted repeated chest infections requiring ventilatory support and was admitted multiple times to the intensive care unit (ICU) of a peripheral hospital. In 2014, primary muscle disease was suspected and the patient was referred to the SQUH ICU. On examination, the boy had normal higher mental and cranial nerve function. However, he had wasting of the spine muscles and could not bend his spine or neck [Figure 1]. His intercostal muscles were weak and he had mild difficulty in getting up, although after standing he was able to walk normally. All deep tendon reflexes were elicited and his serum creatine kinase levels were normal.

An electrocardiogram (ECG) and an echocardiography scan showed normal results; however, myopathy was observed in an electromyogram (EMG). A muscle biopsy was performed and the diagnosis was confirmed by electron microscopy to be a multicore disease in the form of congenital myopathy [Figure 2]. Nicotinamide adenine dinucleotide staining is diagnostic in RSS; however, histochemistry and light microscopy was not possible as the muscle biopsy had very limited muscle tissue. Genetic testing for *SEPN1* was positive. Unfortunately, an MRI scan of the spine could not be arranged before the child was referred back to the peripheral hospital. However, an MRI scan performed on a similarly affected male patient revealed wasting of the paraspinal muscles [Figure 3].

The two children with secondary RSS had mild neck rigidity but demonstrated typical features of the underlying disease with positive Gowers' signs. Both patients were female. One of the secondary RSS patients had mitochondrial myopathy features and was found to have mitochondrial deletion. She had a single heterozygous mutation in the *polymerase gamma (POLG)* gene (c.803G>C, p.268GLyc>Ala), indicating *POLG*-related mitochondrial depletion syndrome. Serum creatine kinase levels were elevated in the first child and normal in the second. The former was initially diagnosed by electron microscopy to have mitochondrial myopathy with a mitochondrial deletion. An EMG was myopathic and nerve conduction was normal. The second patient had features of congenital myopathy although the exact type could not be ascertained. MRI scans of the brain and spine were normal in both cases of secondary RSS.



**Figure 3:** Low signal intensity magnetic resonance image of the spine in a case of paediatric primary rigid spine syndrome. There was wasting of the back muscles of the spine, particularly the erector *spinae*. The muscle tissue was replaced by fibro-fatty tissue (arrowheads).

A representative secondary RSS patient is detailed below.

A five-year-old girl was referred to SQUH from a local orthopaedic hospital in 2014 for an evaluation of foot deformities. Although she had a normal birth and mental and social milestones, her parents noted a delay in motor skill development. On examination, the cranial nerves were normal. Her face had a myopathic look with jaw drop. She had proximal muscle weakness and was positive for Gowers' sign. She had difficulty in bending and turning her neck fully. Both upper and lower limb strength was grade 4/5. Bilateral mild foot inversion with mild weak dorsiflexion of both feet was observed. Her serum creatine kinase level was normal. ECG and echocardiography showed no abnormal findings. The EMG was myopathic and nerve conduction was normal. A muscle biopsy resulted in an initial diagnosis of congenital myopathy, awaiting confirmation via electron microscopy.

## Discussion

There are several childhood muscle dystrophies and congenital myopathies that may present with a rigid spine in the late stages of the primary disease. This is due to the progression of the disease to the paraspinal muscles and is referred to as secondary RSS.<sup>5</sup> In these cases, serum creatine kinase levels may be elevated and the respiratory muscles affected in the terminal stage of the disease.<sup>15</sup> Muscle biopsies and genetic studies help to confirm the diagnosis of the original disease. An MRI scan of the spine does not show the same changes as those seen in primary RSS.<sup>15</sup> Of the two children with secondary RSS in the current study, one had congenital myopathy while the other had mitochondrial myopathy. The latter was

found to have *POLG*-related mitochondrial depletion syndrome; this mutation is pathogenic and has been reported elsewhere.<sup>16</sup>

In primary RSS, the disease starts in the paraspinal muscles and then spreads to the other muscles.<sup>8</sup> Serum creatine kinase levels and echocardiography scans are usually normal in these children.<sup>13</sup> There is no proximal weakness at the onset of the disease and the diagnosis is usually made by features of spine stiffness, an inability for the patient to bend their neck and imaging evidence of the loss of muscle mass in the erector *spinae* muscles.<sup>13</sup> Primary RSS appears to have a genetic basis as mutations in the *SEPN1* gene have been found to be associated with primary RSS, with four siblings mapped to the 1p35-36 chromosome bands.<sup>9,13</sup> However, in a previous cases series of seven children with RSS in Oman, *SEPN1* testing was negative in one patient.<sup>5</sup> In the current study genetic testing for *SEPN1* for one patient was positive. Primary RSS among children is rarely reported in the literature.<sup>12,13</sup> A regional genetic factor may be responsible for the number of primary RSS cases observed in this current single centre study from Oman.

Differential diagnosis of secondary RSS is not difficult as the underlying primary condition often dominates the clinical picture. However, primary RSS needs to be differentiated from other rare conditions such as X-linked Emery-Dreifuss muscular dystrophy, generalised dystonia and stiff person syndrome.<sup>15,17</sup> In cases of Emery-Dreifuss muscular dystrophy, there is proximal wasting of the upper limb muscles with contractures and early cardiac involvement. Serum creatine kinase levels are high and an ECG usually shows abnormal findings.<sup>15</sup> Muscle biopsies and genetic testing are used to confirm the diagnosis. Dystonia can be differentiated from RSS due to the

rigidity of the entire body—as opposed to the localised stiffness seen in RSS—and abnormal posture.<sup>17</sup> Stiff person syndrome may be the initial diagnosis given in cases of primary RSS; indeed, one of the patients in the current study was initially diagnosed with stiff person syndrome while abroad. Generalised body stiffness involving even the abdominal muscles helps in making the correct diagnosis. Stiff person syndrome is very uncommon in children.<sup>17</sup>

Physiotherapy and occupational therapy are the main treatments currently available for RSS. The early involvement of the respiratory muscles in children with primary RSS can be rapid and fatal. In these cases, prompt respiratory care with pulmonary bi-level positive airway pressure non-invasive ventilation—a common mode of respiratory support for patients with respiratory muscle weakness—can prolong life expectancy.<sup>18</sup>

A possible limitation of this study was the fact that histopathological and genetic testing was only performed for a few patients. Further studies are recommended to confirm the histopathological and genetic findings of cases of paediatric RSS in Oman. The development of local advanced genetic facilities is recommended.

## Conclusion

This study aimed to report on cases of RSS among children in Oman. Only 12 children who presented to SQUH during the 18-year study period were reported to have this condition. A total of 10 patients were found to have primary RSS while the remaining two had the secondary form of the disease. As the two forms of this disease have different aetiologies, cases of primary RSS should be differentiated from the secondary type.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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