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The Roberts Syndrome/SC Phocomelia Spectrum—A Case Report of an Adult With Review of the Literature

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Roberts syndrome (RBS) (OMIM #268300) is a rare autosomal recessive disorder characterized by tetraphocomelia (symmetrical limb reduction), craniofacial anomalies, growth retardation, mental retardation, cardiac and renal abnormalities. The syndrome is caused by mutations in the *ESCO2* (establishment of cohesion 1 homolog 2) (Entrez 609353) gene, which is located at 8p21.1, and encodes a protein essential in establishing sister chromatid cohesion during S phase. SC phocomelia (SC) (OMIM #269000), has less severe symmetric limb reduction, flexion contractures of various joints, minor facial anomalies, growth retardation and occasionally, mental retardation. These two syndromes can be considered part of a spectrum, with RBS at the most severe range in which severely affected infants may be stillborn or die in the post-natal period, while individuals with SC phocomelia represent the milder end of the spectrum and typically survive to adulthood. In both presentations, karyotype investigations characteristically reveal premature centromere separation (PCS), otherwise known as heterochromatin repulsion or puffing. There is little literature about the follow-up of adults with the spectrum of RBS/SC phocomelia or their recommended management. We report on an adult presentation of RBS/SC phocomelia spectrum disorder with a history of major cardiac malformation in childhood, normal limbs on physical examination, mild facial anomalies, mild learning difficulties, and PCS. Molecular studies of *ESCO2* have confirmed the diagnosis. A literature review, focussing on adult manifestations of this condition and a discussion of follow-up guidelines are presented.

Key words: phocomelia; adult-middle aged; congenital heart defect; guidelines; Roberts syndrome; SC phocomelia; *ESCO2*

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INTRODUCTION

Roberts syndrome (RBS) (OMIM #268300) is a rare autosomal recessive disorder characterized by tetraphocomelia (symmetrical limb reduction) with craniofacial anomalies, growth retardation, mental retardation, cardiac and renal abnormalities. Karyotype investigations in affected patients characteristically reveal premature centromere separation (PCS), otherwise known as heterochromatin repulsion or puffing. The syndrome is caused by mutations in the *ESCO2* (establishment of cohesion 1 homolog 2) (Entrez 609353) gene, which is located at 8p21.1, and encodes a protein essential in establishing sister chromatid cohesion during S phase [Vega et al., 2005]. SC phocomelia (SC) (OMIM #269000), which was first described in 1969 by Herrmann et al., has a milder phenotype with less severe symmetric limb reduction, flexion contractures of various joints, minor facial anomalies, growth retardation, and possibly mental retardation [Herrmann et al., 1969; Schule et al., 2005]. SC is also inherited in an autosomal recessive manner and exhibits PCS. The two syndromes can be considered part of a spectrum, with RBS representing the most severe presentation and SC phocomelia at the milder end of the spectrum. Individuals with SC typically survive to adulthood

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whereas severely affected RBS infants may be stillborn or die in the post-natal period [Van Den Berg and Francke, 1993]. There is little literature about the follow-up of adults with this spectrum of RBS/SC phocomelia or the recommended surveillance and management of this condition.

In this report, we describe an adult with a cardiac defect requiring surgery and his subsequent clinical and molecular diagnosis of RBS/SC phocomelia. We review the published adult cases and suggest guidelines for management of adults with RBS/SC phocomelia.

PATIENT

A 31-year-old male presented to the Adult Genetics clinic for assessment after being referred for a query diagnosis of Noonan syndrome given his history of short stature and subaortic stenosis. He was diagnosed with subaortic stenosis at the age of 8 years, following a syncopal episode, and underwent resection of the fibromuscular subaortic stenosis. At age 14, cardiac evaluation revealed recurrence of his left ventricular outflow gradient: he had a balloon valvuloplasty and dilatation of the residual subaortic stenosis. Investigations at age 22 revealed a left ventricular outflow tract mean gradient of 39 mmHg. He had catheterization and a coronary angiogram at that time was normal. Since recent MRI investigations demonstrated recurrence of subaortic stenosis with an aortic valve surface area of 0.84 cm^2, a peak transvalvular gradient of 86 mmHg, and moderate to severe aortic regurgitation, he underwent a repeat subaortic stenosis resection. His post-operative course was complicated by complete heart block requiring permanent pacemaker insertion. His other medical issues include dental crowding, for which he had eight teeth extracted. He had mild learning difficulties but completed a college course in architectural design. He currently lives with his parents, a non-consanguineous Italian couple. He has a healthy younger sister. The remainder of the family history is non-contributory. His birth weight was 2.1 kg (<3rd centile). The remainder of the birth parameters were unavailable.

On physical examination, he has short stature (153 cm <3rd centile, at the 50th centile for an 11-year-old male) and dysmorphic features included hypertelorism, down-slanting palpebral fissures, a prominent nasal bridge, hypoplastic alae nasi, and subsequent appearance of a prominent columella (Fig. 1). His ears are simply formed and slightly posteriorly angulated. He has a high narrow palate and mild retrognathia. There is no posterior redundancy of neck. The nipples are normally placed. Examination of the chest and abdomen are unremarkable. Extremity examination revealed normal thumbs, fingers, and toes. The weight is 60 kg, just below the 50th centile for an adult male. The head circumference measures 54 cm (10th centile). The upper arms measure 26.5 cm (<3rd centile and 50th centile for an 8-year-old male), the forearms 22.5 cm (5th centile and 50th centile for a 10.5-year-old male), the thighs 34.5 cm (−2 SD or 50th centile for 9.5-year-old male), the lower legs 35 cm (<5th or 50th centile for 11-year-old male), the hand length, 18.8 cm (<50th centile for adult male), the palm length 10.5 cm (right) and 10.8 cm (left) (<50th centile for adult male) and the foot length is 22.5 cm (right) and 23 cm (left) (<5th centile, 50th for 11-year-old male). The arm span is 150 cm, with an arm span to height ratio of 0.98. The upper-to-lower-segment ratio is 1.06, confirming the shortening of the leg bones. There were no joint contractures noted. The thumbs are noted to be broad bilaterally.

Genetic assessment included karyotype, sequencing of the *PTPN11*, *SOS1*, and *KRAS* genes and FISH analysis for 22q11.2 [Vysis HIRA] microdeletion syndrome were normal. Karyotype revealed PCS in all metaphases. PCS, also known as "heterochromatin repulsion" (HR), is an abnormality of sister chromatid apposition around the centromere, which is particularly noticeable for those chromosomes with large blocks

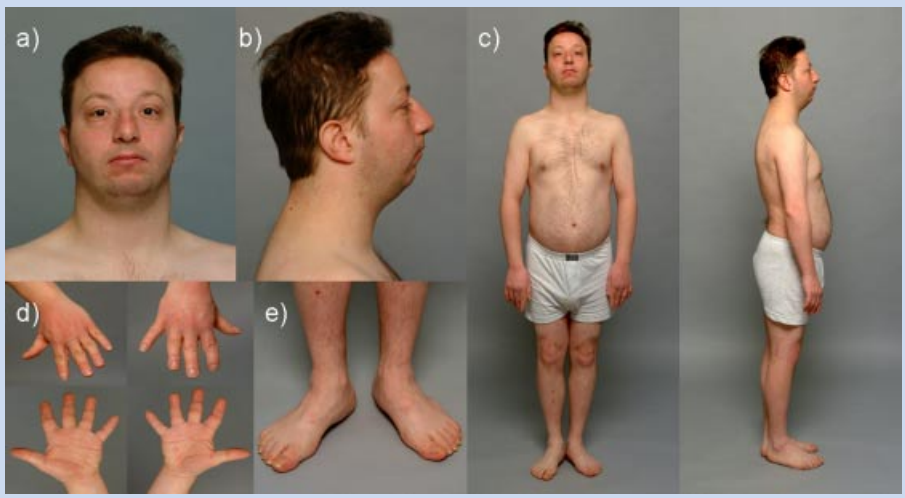

FIG. 1. a: Facial features of proband. Note the hypertelorism, down-slanting palpebral fissures, a prominent nose, and hypoplastic alae nasi. b: Mild retrognathia is seen on a lateral view. c: Full body profile showing length of arms and legs. d,e: Images of the proband's left and right hands, as well as his toes showing brachyphalangia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of heterochromatin (chromosomes 9 and 16). It is best seen in C-stained chromosomes (Fig. 2). This was diagnostic for RBS/SC. There were no abnormal mitotic figures noted.

Following the diagnosis, a skeletal survey was conducted. It showed no limb reduction defects, but evidence of hypertelorism, mild brachymetacarpalia, brachyphalangy, and short femoral necks. Evidence of old, untreated right developmental dysplasia of the hip was also seen (Fig. 3). Other investigations included abdominal/pelvic ultrasound and an ophthalmological evaluation, which were both normal.

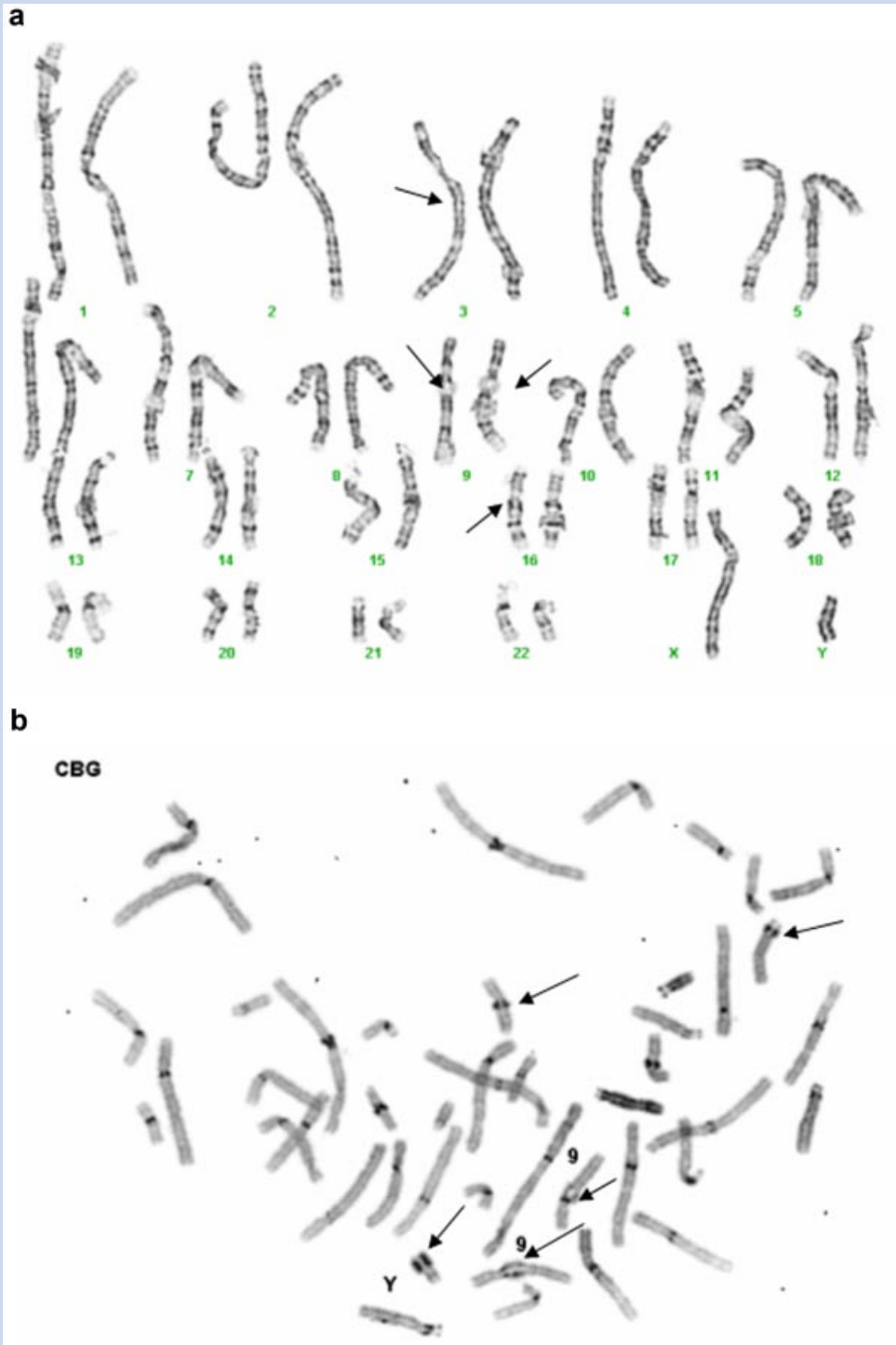

FIG. 2. a: G-banding (resolution 550) with puffing at the centromeres and heterochromatic regions. b: C-staining technique showing separation of the heterochromatic regions (heterochromatin repulsion) as indicated by the arrows.

FIG. 3. Skeletal survey composite (a) showing hypertelorism, (b) evidence of mild brachymetacarpalia and brachyphalangia, (c) no obvious limb reduction defects of the long bones in both the upper and lower extremities, (d) evidence of old, untreated right developmental dysplasia of the hip, (e) short femoral necks, (f) normal feet.

Mutational analysis of the *ESCO2* gene was performed by PCR amplication followed by direct sequencing of the coding exons (2–11) in both directions through the Mount Sinai Genetic Testing Laboratory [Mount Sinai School of Medicine, New York, NY]. The sequence of the primers used for *ESCO2* PCR amplification and sequencing are available upon request. Mutational analysis of *ESCO2* revealed a homozygous mutation for p.V56KfsX6 (c.166_170delGTTTT), predicted to result in a severely truncated protein (electropherogram showing the mutation can be seen as supporting information Figure 1 which may be found in the online version of this article).

DISCUSSION

To our knowledge, this is the first case report of an individual with normal appearing, shortened limbs diagnosed with RBS/SC phocomelia whose congenital cardiac abnormality required several surgeries, but has not affected his survival into adulthood. The homozygous mutation found in *ESCO2* causes a severely truncated protein to be produced. Protein truncations are the most common type of mutations described in *ESCO2* to date [Vega et al., 2009]. The mutation in our propositus has not been reported in the literature and appears to be the most proximal to the 5′ end compared to all others reported thus far.

Our review of the medical literature has identified nine other reported adult cases. Their characteristic clinical findings and "RS rating" for quantifying the severity of the syndrome as reported by Van Den Berg and Francke [1993] are described in Table I. The characteristic clinical features of RBS/SC phocomelia were present in the majority of adult patients: limb anomalies (9/10), craniofacial anomalies (8/10), growth retardation (10/10), mental retardation/learning difficulties (7/10).

In total 2/10 adult patients were identified with major cardiac congenital anomalies, both with aortic stenosis. While our patient remains well after three surgeries, the other patient died at age 23 of congestive heart failure and aspiration pneumonia, after an echocardiogram showed an apical aneurysm in the left ventricle and an apical thrombus [Herrmann et al., 1969]. The remaining cases were not known to have major cardiac abnormalities, although one patient has a grade 2/6 systolic ejection murmur.

With respect to his "RS rating," our propositus ranked the fourth highest in severity out of the ten adult cases with a rating of −0.50 (Table I). Van Den Berg and Francke reported the "RS rating" for quantifying the severity of RBS/SC phocomelia. The rating system was based on six criteria including growth retardation, phocomelia of the arms, phocomelia of the legs, survival beyond 1 month of age, palatal clefting, and craniofacial abnormalities. RS rating scores >0.5 were classified as individuals with multiple severe malformations. Patients who had a combination of both severe and mild malformations have a score between −0.5 and 0.5. Patients with multiple mild malformations had scores <−0.5 [Van Den Berg and Francke, 1993]. However, it should be noted that cardiac defects do not factor into the RS rating scale, despite the presence of a heart defect in 21 of the 43 cases that were recorded in the series, or 48.8% [Van Den Berg and Francke, 1993].

The current case not only highlights the variability in the RBS/SC phocomelia spectrum but also demonstrates that clinically apparent limb anomaly may not be an obligate feature for the diagnosis of this condition and that careful measurements may be required to detect subclinical limb shortening. Although, our proband did not have the severe limb manifestations of RBS, upon

TABLE I. Adult Manifestations of Roberts Syndrome/SC Phocomelia in the Literature

	Current propositus 1	O'Brien and Mustard [1921] 2[a]	Herrmann et al. [1969] 3[b]	Petrinelli et al. [1984] 4[c]	Parry et al. [1986]—Patient 1 5[d]	Parry et al. [1986]—Patient 2 6[e]	Maserati et al. [1991] 7[f]	Schule et al. [2005] 8[g]	Holden et al. [1992] 9	Hasegawa et al. [1998] 10
General										
Sex	M	M	M	F	F	F	F	M	M	F
Age	31	29	23 when died	29	34 when died	43 when died	23	31	18	45
Growth retardation	+	+	+	+	+	+	+	+	+	+
Mental retardation	+−	+−	++	−	+−	+−	−	+−	−	++
Skin/hair	Dry skin	NR	Fine silvery hair	NR	NR	NR	NR	NR	Sparse silvery-blonde hair	NR
Craniofacial anomalies										
Microcephaly	−	+	+	−	+	+	−	+	+	+
Hemangioma	−	−	+	NR	+	−	NR	NR	NR	NR
Prominent eyes	−	+−	−	+	−	−	NR	+	NR	NR
Hypertelorism	+	+	+	NR	−	−	NR	NR	+	NR
Cloudy cornea	NR	−	−	−	NR	NR	NR	+−	NR	NR
Wide nasal bridge	+	−	NR	−	−	−	NR	NR	NR	NR
Hypoplastic nasal alae	+	NR	+	+	+	+	NR	NR	NR	NR
Cleft palate/lip or high arched palate	High arched	High arched	−	High arched	−		−	−	+	High arched
Micrognathia/retrognathia	+	NR	−	+	−	+	NR	NR	+	NR
Prominent maxilla	−	+−	−	NR	+	+	NR	NR	NR	NR
Limb anomalies										
Phocomelia	2	4	4	2	4	4	4	4	4	0
Number of fingers	5	3	5	5	4	4	6/5	4/5	5	5
Humeral hypoplasia	−	Aplasia	−	+	+	+	NR	+	−	−
Ulnar hypoplasia	−	Aplasia	Aplasia	+	+	+	+	+	Aplasia	−
Radial hypoplasia	−	Aplasia	Aplasia	+	Aplasia	Aplasia	Aplasia	+	Aplasia	−
Arm bone synostosis	−	−	NR	+	−	+	NR	NR	NR	−
Number of toes	5	5	5	5	5	5	NR	NR	5	5
Femural hypoplasia	+	+	−	−	−	−	Aplasia	+	−	−
Tibial hypoplasia	−	Aplasia	−	−	+	+	+	+	+	−
Fibular hypoplasia	−	Aplasia	Aplasia	−	+	+	+	+	Aplasia/ hypoplasia	−
Leg bone synostosis	−	−	NR	−	NR	NR	NR	NR	+	−
Syndactyly	−	+	+	−	−	−	−	NR	−	−
Flexion contractures	−	NR	+	+	+	+	NR	+	+	−
Other anomalies										
Cardiac abnormalities	+	−	+	NR	NR	−	NR	−	−	NR
Renal abnormalities	−	−	−	NR	+	−	NR	−	−	NR
Miscarriage	N/A	N/A	N/A	+	−	+	NR	N/A	N/A	−
Cancer	−	NR	NR	NR	+	NR	NR	NR	NR	NR
Venoocclusive disorder	−	NR	+	NR	−	+	NR	NR	NR	+
Facial palsies	−	NR	NR	NR	+	+	NR	NR	NR	+
Diagnostic features										

(*Continued*)

careful examination, the etiology of his short stature was likely a combination of growth failure associated with this condition and shortening of the long bones. His proximal long bones were more involved than the distal long bones. Also, he has survived to adulthood despite significant subaortic stenosis requiring surgery and is functioning at a normal level despite initial learning difficulties.

In addition to the characteristic features of RBS/SC phocomelia, several other common features were noted in the adult cases. These other features included: spontaneous pregnancy loss (2/5 patients) [Petrinelli et al., 1984; Patient 2—Parry et al., 1986], (2) ocular findings beyond corneal clouding (3/9 patients) [Herrmann et al., 1969; Parry et al., 1986], (3) cancer (1/10 patients) [Parry et al., 1986], and (4) thrombosis (2/10 patients) [Parry et al., 1986; Feingold, 1992].

Of the five female adults, three were reported to have had pregnancies. Patient 1 in Parry et al. [1986] (Patient 5 in this review) achieved a full term pregnancy. However, Patient 2 in Parry et al. [1986] (Patient 6) and the patient reported in Petrinelli et al. [1984] (Patient 4) both had spontaneous pregnancy loss, the former in the second trimester and the latter in the first trimester. It is not clear whether this is related to RBS/SC phocomelia or whether these were from other causes. Patient 6 also died of a massive stroke [Parry et al., 1986]; therefore, there could have been an underlying prothrombotic risk leading to the spontaneous abortion in the second trimester. The first trimester loss in Patient 4 may be similar to the risk in the general population [Petrinelli et al., 1984]. Patient 10 was found to be mosaic for Turner syndrome in 10/50 cells analyzed and never became pregnant [Hasegawa et al., 1998]. Regardless of the cause, awareness should be present about the possibility of spontaneous loss in female patients with RBS/SC.

Ocular findings in the cases reported by Parry et al. [1986] and Herrmann et al. [1969] differ from the corneal clouding reported in Van Den Berg and Francke's [1993] review of cases. Cavernous hemangioma of the optic nerve (Patient 3), paracentral scotoma and pits of the optic nerve (Patient 5), tilting of the optic nerve (Patient 6), and bilateral optic nerve atrophy (Patient 10) were examples of manifestations in adults with RBS/SC phocomelia according to this review [Herrmann et al., 1969; Parry et al., 1986; Feingold, 1992; Hasegawa et al., 1998]. Continued ophthalmologic follow-up is suggested in patients with RBS/SC.

Cancer risk may be increased as RBS/SC patients are surviving beyond childhood [Schule et al., 2005]. From this review, only Patient 5 developed malignant melanoma [Parry et al., 1986]. This risk may be under-reported, as there are no records of the possibility of malignancy in the other five reported cases in the literature. Longer follow-up and awareness of this possibility is needed to determine whether there is in fact an association with malignancy and RBS/SC.

Finally, the existence of MoyaMoya disease with multiple minor strokes and a myocardial infarction in the patient reported by Herrmann et al. [1969] (Patient 3), and the development of a massive stroke and second trimester pregnancy loss in Patient 2 from Parry et al. [1986] (Patient 5), suggest that adult patients with RBS/SC may be at an increased risk for venoocclusive disease. Attempts should be made to modify known atherosclerotic risk factors so that they do not have an additive effect if thrombosis is

TABLE I (*Continued*)

	Current proposita	O'Brien and Mustard [1921]	Herrmann et al. [1969]	Petrinelli et al. [1984]	Parry et al. [1986]—Patient 1	Parry et al. [1986]—Patient 2	Maserati et al. [1991]	Schule et al. [2005]	Holden et al. [1992]	Hasegawa et al. [1998]
	1	2[a]	3[b]	4[c]	5[d]	6[e]	7[f]	8[g]	9	10
Premature centromere separation	+	NR	+	+	+	NR	+	+	+	+
RS rating score	−0.50	−0.17	−1.00	−1.20	−0.83	−0.83	−1.00	−0.17	0.83	−1.00
Mutation (if known)	Homozygous for c.166_170delG TTTT of *ESCO2* causing a severely truncated protein p.V56KfsX6		c.751_752insA causing p.K253fsX26 frameshift mutation		c.604C → T causing p.Q202X (non-sense); c.752delA causing p.K253fsX12 (frameshift and protein truncation)			c.1131 + 1G → A causing p.R338fsX17 splice-site mutation	Mutation reported in Gordillo et al. [2008]	

+, Feature is present; −, feature is absent; NR, not recorded/documented; N/A, not applicable; + −, mild phenotype; ++, moderate phenotype; +++, severe phenotype.
[a]Presented as case 8 Van Den Berg and Francke [1993].
[b]Clinical follow-up by Feingold [1992] and presented as case 19 in Van Den Berg and Francke [1993] and Patient 3 Family 1 in Schule et al. [2005].
[c]Presented as case 64 in Van Den Berg and Francke [1993].
[d]Presented as part of Family 2—proband in Schule et al. [2005], case 67 in Van Den Berg and Francke [1993].
[e]Presented as part of Family 2—sibling in Schule et al. [2005], case 68 in Van Den Berg and Francke [1993].
[f]Presented as case 93 in Van Den Berg and Francke [1993].
[g]Presented as case 100 in Van Den Berg and Francke [1993].

indeed increased in patients with RBS/SC. Of note is Patient 10 who developed cerebellar hemorrhage. She also had high signal intensity areas on brain MRI bilaterally in the thalamus, putamen, and white matter in T2 weighted images. The etiology of these findings is unknown and the significance of these findings for patients with RBS/SC is unclear.

Of note is a single adult case that presented with periodic hypersomnia [Hasegawa et al., 1998]. It is unclear whether this presentation is related to RBS/SC or another etiology. A clinical sleep study may be warranted if there is suggestion of a sleep disturbance.

The follow-up of more adults with RBS/SC is needed to determine how to best counsel for potential risks and management for adult manifestations of RBS/SC. Based on this review, we recommend close surveillance during pregnancy for possible spontaneous loss, continued ophthalmological follow-up, careful screening for cancer and alteration of risk factors for venoocclusive disease in patients with RBS/SC who survive to adulthood.

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