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Clinical Report

Long-Term Follow-Up in Stuve–Wiedemann Syndrome: A Clinical Report

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Stuve–Wiedemann syndrome (SWS) is an autosomal recessively inherited disorder that is usually associated with high mortality in the neonatal period. Eleven cases have been published with prolonged survival, the oldest being 16 years. This phenotype is characterized by progressive skeletal anomalies including short stature, severe spinal deformities, bowing of the long bones, contractures and spontaneous fractures, and by neurological features that resemble dysautonomia. Here we report on the natural history of a Portuguese girl from birth till 12 years. The diagnosis was molecularly confirmed by the detection of a homozygous 4 bp deletion (167_170 del TAAC) in exon 3 of *LIFR*. We compare the findings in this patient to other patients with prolonged survival from the literature. © 2008 Wiley-Liss, Inc.

Key words: Stuve–Wiedemann syndrome; Schwartz–Jampel syndrome; *LIFR* gene; natural history

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INTRODUCTION

The Stuve–Wiedemann syndrome (SWS) is a rare autosomal recessive entity, characterized by a congenital bone dysplasia and autonomous dysregulation [Stuve and Wiedemann, 1996]. Patients usually present in the neonatal period with respiratory problems, feeding and swallowing difficulties, recurrent episodes of hyperthermia, bowing of long bones and camptodactyly with ulnar deviation of the hands. Radiological features include bowed femurs, tibiae, and fibulae, and wide metaphyses with abnormal trabecular pattern [Al-Gazali et al., 1996; Chabrol et al., 1997; Cormier-Daire et al., 1998a]. The disorder has been considered lethal in the neonatal period until Kozlowski and Tenconi [1996] reported of a boy surviving beyond 3 years. Since then, 11 survivors have been described [Kozlowski and Tenconi, 1996; Giedion et al., 1997; Chen et al., 2001; Navarrete Faubel et al., 2002; Reed et al., 2002; Al-Gazali et al., 2003; Di Rocco et al., 2003; Reither et al., 2006]. Superti-Furga et al. [1998] reported follow-up of two previously published cases [Kozlowski and Tenconi, 1996; Giedion et al., 1997]. The clinical and radiological symptoms overlapped with Schwartz–Jampel syndrome type 2 (SJS2) suggesting the entities to be allelic [Cormier-Daire et al., 1998b; Superti-Furga et al., 1998]. Indeed both SWS and SJS2 were subsequently found to be caused by mutations in the Leukaemia Inhibitory Factor Receptor (*LIFR*) gene [Dagoneau et al., 2004].

Here, we report on the long-term follow-up of a 12-year-old Portuguese girl with molecularly

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confirmed SWS, to further illustrate the natural history of the non-lethal form of the disorder, and we compare her findings to those from literature.

CLINICAL REPORT

The proposita is the first-born child of consanguineous (first cousins) parents of Portuguese Gypsy origin. The couple had a subsequent child who died in the neonatal period due to respiratory failure and cardiac disease. Their third child was healthy, and a recently newborn fourth child was also affected.

The pregnancy was uneventful; delivery at term was by breech presentation. Weight at birth was 3,000 g (25th centile), length was 47 cm (10th centile), and head circumference was 33 cm (2nd centile). Apgar scores were 7 and 5 after 1 and 5 min, respectively. On the second day she developed partial seizures that were controlled with phenobarbital. She was found to be hypotonic, and to have facial myotonia, especially evident by the pursed appearance of her mouth and incomplete closure of the palpebral fissures. When crying her face became asymmetrical. She had low-set ears, a short neck, short and somewhat bowed limbs, and contractures of elbows and knees, camptodactyly of all fingers and talipes equinovarus. She was a poor feeder, with a weak swallowing reflex necessitating tube feeding for 3 months. She experienced unexplained recurrent bouts of fever from the first week of life on.

At 4 months, she developed respiratory distress during an episode of hyperthermia and had an unusually severe bacterial conjunctivitis resulting in hospital admission. During the remainder of the first year of life, she was repeatedly readmitted because of periods of unexplained fever. These were accompanied by respiratory problems that led to respiratory insufficiency, pulmonary infections, and the necessity for artificial ventilation. These problems were thought to be in part explained by a reduced swallowing reflex, facial myotonia, and peripheral hypotonia.

At 1 year, her length was 66.8 cm (<5th centile), weight was 6,400 g (<5th centile), and head circumference was 44.5 cm (10th centile). She had delayed development of motor milestones but normal cognitive development. Her limbs were short, joints were prominent, lower limbs were bowed, and there were still contractures of elbows and knees. She had bouts of excessive sweating and poor temperature regulation, bit her tongue repetitively resulting in ulcers, and had reduced pain sensitivity.

At $2^{10}/_{12}$ years, she could stand but not walk. Her cognitive development was excellent. She had bilateral corneal opacities and ulnar deviation of the hands. In the ensuing years she had poor body temperature regulation, with asymmetric and paradoxical sweating, and areas of hypoperfusion and hyperperfusion of trunk and extremities.

At 6 years, she was 100 cm (<5th centile) tall. Her face was asymmetrical and somewhat squarely-shaped especially due to a broad lower 1/3rd of her face, and she showed frontal bossing, large eyes, bilateral cornea opacities, absent corneal reflexes, anteverted nares, smooth tongue, poor dentition with chronic dental abscesses, retrognathia and a short neck. Her voice was hoarse and nasal. She had a progressive scoliosis of the spine, enlarged and prominent joints with contractures at the elbows, fingers and knees, short thumbs, clubbing of the nails, and chronic dislocation of the left patella. The skin of her chest and upper arms showed prominent and tortuous veins.

Around 9 years she gradually lost her ability to walk, mainly due to progressive decrease in knee mobility and increase in bowing of her legs, and she became wheelchair dependent. At 10 years she had fine hair, a generalized thin skin, excessive sweating, the mobility in her elbows, fingers, and knees had become further restricted, bowing of the lower legs remained unchanged, patella luxation was present bilaterally, and the kyphoscoliosis had become severe. Pulse was never found to be irregular and she had no orthostatic hypotension.

She was last investigated at 12 years. Height was 120 cm (<5th centile), and weight was 30 kg (5th centile). Her phenotype had remained unchanged in the last 2 years, except that the facial myotonia had become present again from time to time, showing in pursed lips. Shedding of her primary dentition was delayed. There was some development of mammary glands but no menarche. The clubbed and deformed fingers prevented her from writing any longer, so she needed computer assistance for this. It had become impossible for her to wear shoes.

The most salient clinical features are shown in Figures 1–5.

Additional Investigations

A complete blood analysis which included coagulation, metabolic, endocrine, and immunological studies were normal. Serum alkaline phosphatase levels (1,569 U/L; normal values 145–420 U/L), urinary excretion of hydroxyproline (2,279 μmol/mmol creatinine; normal values 31–106 μmol/mmol creatinine), and total serum proline levels (1,803 μmol/24 hr; normal values 48–420 μmol/24 hr) were all elevated, probably secondary to increased osteoclast activity. Repeated cerebral, cardiac, abdominal and renal ultrasounds at various ages gave all normal results. Chromosome analysis gave a normal female karyotype (46,XX), and results of respiratory and sleep studies were normal. Ophthalmologic evaluation was performed repeatedly: at 5 months the first unilateral cornea ulcer was noticed, at 9 months a lack of corneal reflexes, bilateral corneal ulcera and opacities became

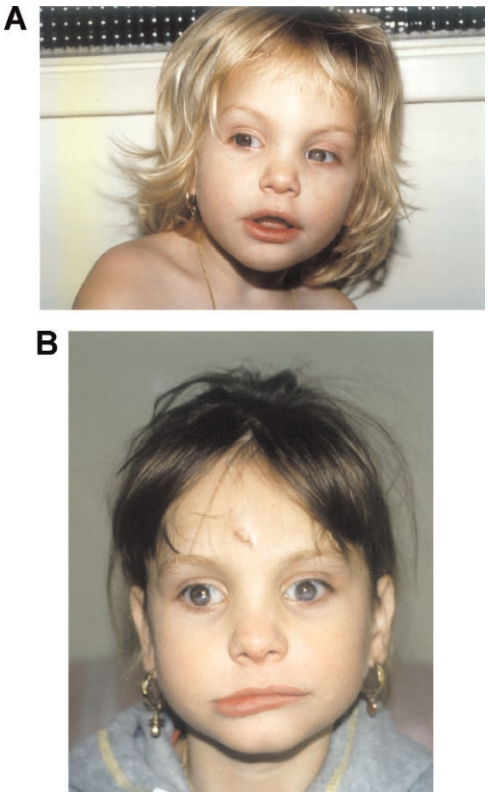

FIG. 1. Face of the proposita at 3 years (**A**) and 10 years (**B**). Note the partial bilateral cornea opacities at 3 years and complete opacities at 10 years. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

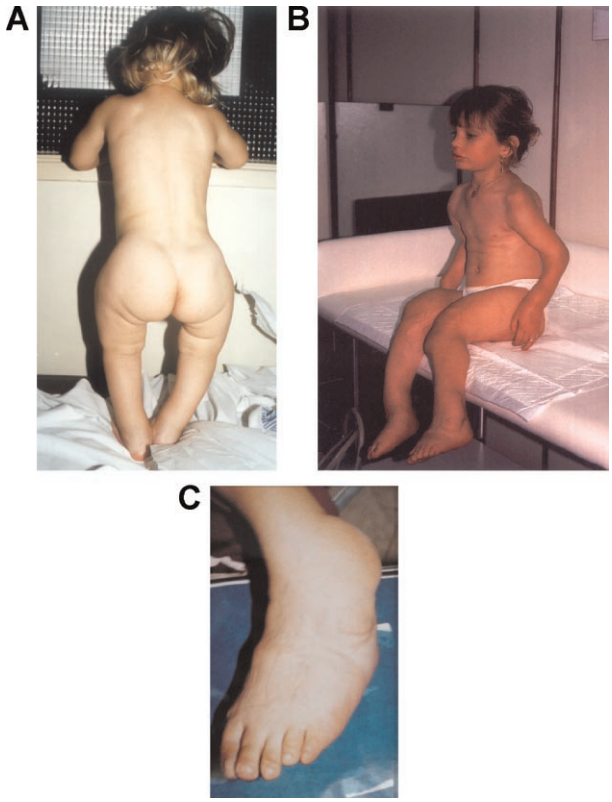

FIG. 3. Proposita at 3 years (**A**), 6 years (**B**), and 12 years (**C**). Limbs are short and bowed at first, and show more prominent joints and contractures with 6 years, which becomes more prominent with 12 years. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

evident, at 12 months this lead to bilateral leukomas, hindering vision severely.

Molecular analysis of the *LIFR* gene was performed as previously described [Dagoneau et al., 2004], and revealed homozygosity for a 4 base deletion in exon 3 (NM_002310: c.167_170delTAAC). Parents were heterozygous for this mutation. The youngest brother was also homozygous for the mutation. The deletion is located in the region encoding the CRH1 domain and is responsible for a premature termination of translation 53 amino acids downstream.

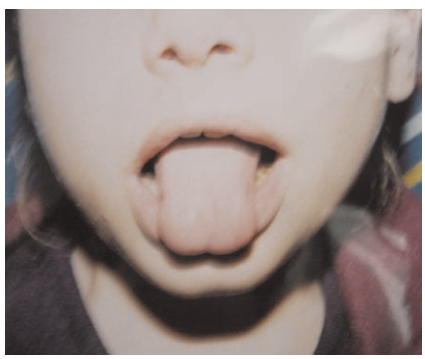

FIG. 2. Smooth tongue of the proposita at 12 years. A tongue tie makes the tongue somewhat bifid. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

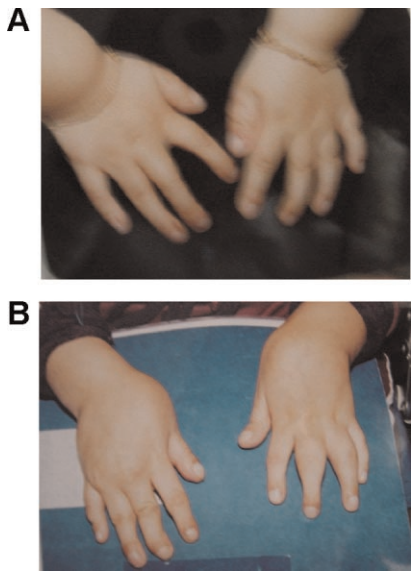

FIG. 4. Hands at 3 years (**A**) and 12 years (**B**) showing progressive ulnar deviation, swelling of the finger joints and development of contractures by 12 years. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

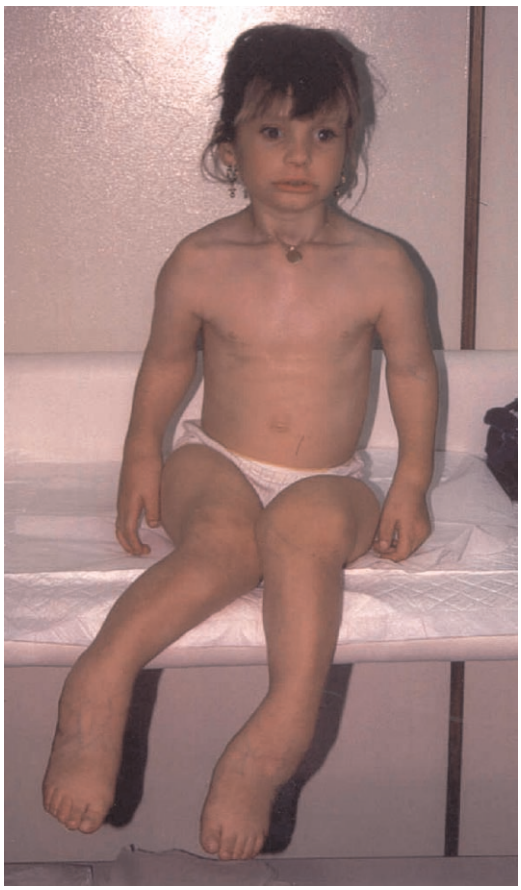

FIG. 5. Skin of the proposita at 6 years showing generalized prominently tortuous veins. Please note the patella dislocation on the left. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

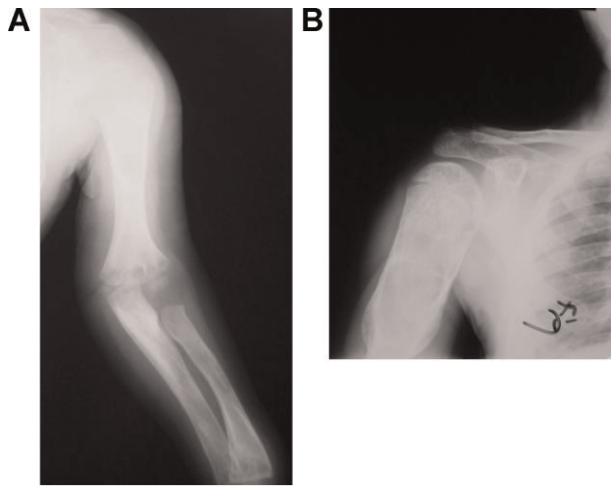

FIG. 6. Radiograph of upper limb of the proposita at 3 years (**A**) and 11 years (**B**). Note the progressive widening and deformation of metaphyses and diaphyses, irregular trabeculation, and cystic changes. At 11 years the remnants of an old femur fracture are visible.

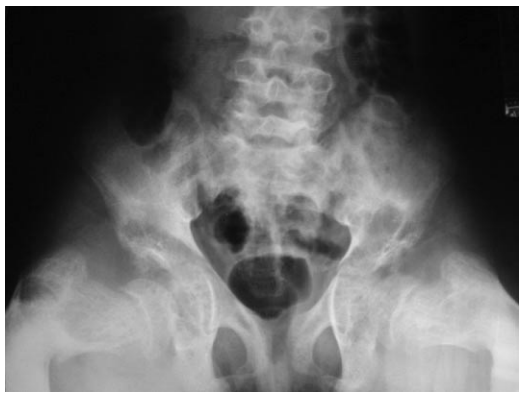

FIG. 7. Pelvic radiograph at 11 years. Note the triangular pelvis, dysplastic acetabulum, bilateral coxa vara, angulation of the femoral diaphyses and sclerosis of the internal cortex. On the left there is a subtrochanteric cystic change visible.

Radiological surveys have been performed at several ages. The most salient findings are shown in Figures 6–11 and their description is provided in the legends.

DISCUSSION

We described the natural history of a girl with SWS. Her findings were compared to other long-term survivors from literature in Table I. In the following text we describe the major features of the natural history SWS.

Prenatal signs in SWS patients detected by ultrasonography have been short and bowed femora, talipes equinovarus, and reduced fetal movements and oligohydramnios.

At *birth*, SWS patients have a characteristic face characterized by midface hypoplasia, a short nose with a wide nasal base. They may show pursed lips, but the intensity of myotonia is variable. Myotonia decreases with time in the first two years. All have

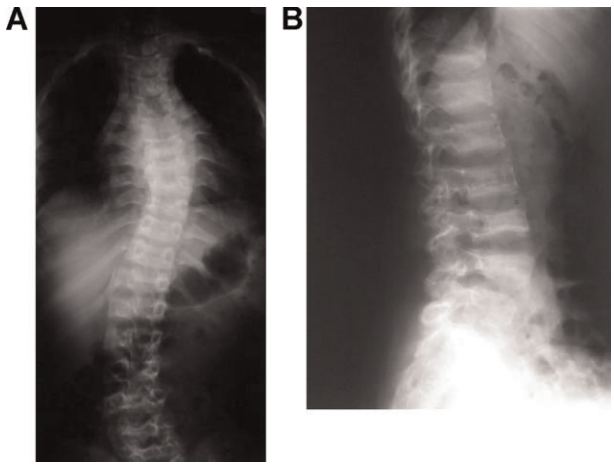

FIG. 8. Spinal radiographs at 11 years. Note the osteopenia and compression of several vertebral bodies which are concave and wedge-shaped.

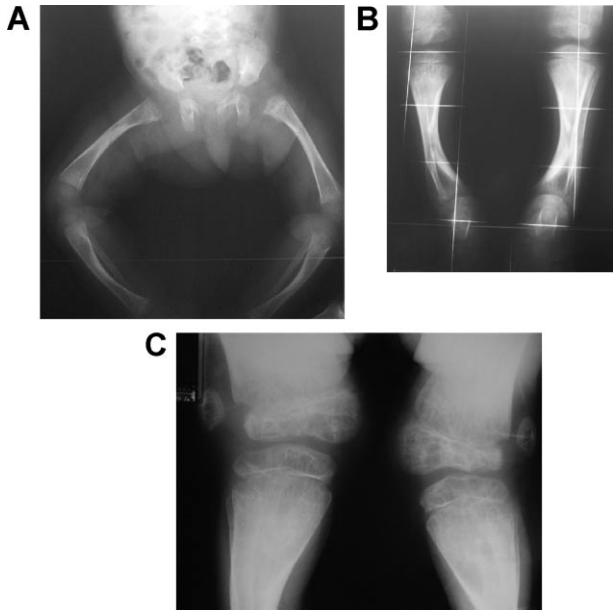

FIG. 9. Radiograph of lower limbs at 2 months (**A**), 3 years (**B**), and 11 years (**C**). Note the progressive bowing of long bones, internal cortical thickening at the concave site, involvement of fibula from 6 years on, enlarged distal metaphyses, and irregular trabeculation. At 11 years there are cystic changes in tibia and fibula, osteopenia, and fragmentation of epiphyses.

short and bowed limbs and frequently a limited mobility in elbows, knees, feet, and fingers is found.

The *general course* is characterized by swallowing problems necessitating tube feeding for extended periods of time, repeated aspirations and pulmonary infections. Gradually hyperthermia and other dysautonomic symptoms arise, and the skeletal signs and

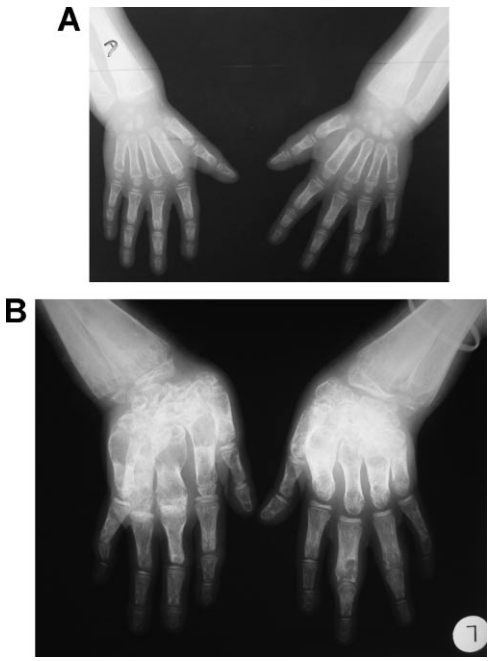

FIG. 10. Hand radiograph at 3 (**A**) and 11 years (**B**). Note ulnar deviation of the hand, progressive enlargement of distal metaphyses and progressive cystic changes in metacarpals. Cortical density becomes reduced.

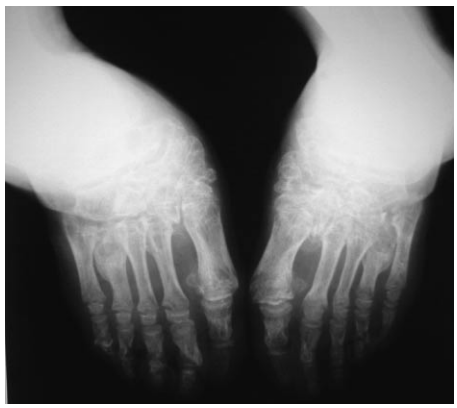

FIG. 11. Feet radiograph at 11 years showing osteopenia and widened metatarsal bones.

symptoms become worse with an inhibit mobility. Cognitive development is normal.

Symptoms of *dysautonomia* include temperature instability, excessive and sometimes paradoxical sweating, reduced pain sensation, absent corneal reflex, and reduced or absent patellar reflexes. As in other forms of disturbed pain sensation this causes

TABLE I. Major Findings in Long-Term Survivors With Stuve–Wiedemann Syndrome, Compared to the Findings in the Present Patient

Feature	Proposita	Patients
Consanguinity	+	4/11
Gender/age	12 Y/F	8M/3F
Reduced fetal movements		4/11
Oligohydramnios		3/11
Facial		
Midface hypoplasia	+	5/11
Square jaw	+	5/11
Short, wide nose	+	5/11
Pursed mouth	+	4/11
Leukoma/keratitis of cornea	+	2/11
Feeding problems	+	9/11
Infections	+	5/11
Dysautonomia		
Poor temperature regulation	+	9/11
Paradoxical sweating	+	2/11
Decreased lacrimation	−	1/11
Smooth tongue	+	5/11
Tongue ulcerations	+	5/11
Reduced pain sensation	+	6/11
Absent corneal reflex	+	6/11
Hyporeflexia	+	3/11
Skeletal		
Short stature	+	10/11
Short and bowed limbs	+	11/11
Enlarged joints	+	7/11
Contractures	+	8/11
Camptodactyly		2/11
Spine deformity	+	7/11
Fractures	+	6/11
Radiological		
Osteoporosis	+	8/11
Short and bowed long bones	+	10/11
Diaphyseal undertubulation	+	8/11
Metaphyseal rarefaction	+	9/11
Destruction of femoral heads	−	2/11

repeated injuries and subsequently is responsible for infections of eyes, gingiva, tongue, and limbs. Secondary phenomena are cornea opacities, early dental loss, a smooth and deformed tongue, and possibly the frequent fractures are related too.

Skeletal findings are present in all survivors. They are progressive: short stature, bowing and shortening of all limbs, enlarged joints, contractures in at least elbows, knees and fingers, and scoliosis with or without hyperlordosis. Recurrent fractures are secondary to the osteopenia and possibly to the dysautonomia. At a later stage, luxation of patellae occurs.

Radiography shows progressive bowing of tubular bones, starting at femora and tibiae and to a lesser extent metacarpals, and gradually also involving upper limbs, and irregular and enlarged metaphyses with abnormal trabecular pattern are invariably present. The fibulae remain normal. Osteopenia gradually becomes more widespread, including vertebral bodies, ribs and long bones. The vertebrae also flatten with time and become wedge-shaped and compressed.

At present, *management* is symptomatic: intensive care in infancy for the swallowing problems and inevitable aspirations, early protection of eyes against repeated trauma (including sunlight) to prevent visual loss, physical therapy and pediatric orthopedics for contractures and scoliosis to allow the best possible mobility, early recognition and adequate treatment of fractures, and recognition of the signs of autonomic dysfunction, which only need treatment if expressed, such as in severe hyperthermia.

We conclude that the major symptoms influencing daily life in patients with SWS who survive are loss of vision, paradoxical sweating/shivering, severe spinal deformity, spontaneous fractures and limitations in mobility. There is no information available on the natural history in adulthood. Hopefully with time further studies, which have become possible after the identification of the disease causing gene, will allow alteration in the natural history of this devastating disorder.

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