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Adults With Sotos Syndrome: Review of 21 Adults With Molecularly Confirmed *NSD1* Alterations, Including a Detailed Case Report of the Oldest Person

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Sotos syndrome is a well-described multiple anomaly syndrome characterized by overgrowth, distinctive craniofacial appearance, and variable learning disabilities. The diagnosis of Sotos syndrome relied solely on these clinical criteria until haploinsufficiency of the *NSD1* gene was identified as causative. We describe a 63-year-old woman with classic features and a pathogenic *NSD1* mutation, who we believe to be the oldest reported person with Sotos syndrome. She is notable for the diagnosis of Sotos syndrome late in life, mild cognitive limitation, and chronic kidney disease attributed to fibromuscular dysplasia for which she recently received a transplant. She has basal cell and squamous cell carcinoma for which her lifetime of sun exposure and fair cutaneous phototype are viewed as risk factors. We also reviewed previous literature reports (n = 11) for adults with Sotos syndrome, and studied patients ascertained in the Spanish Overgrowth Syndrome Registry (n = 15). Analysis was limited to 21/27 (78%) total patients who had molecular confirmation of Sotos syndrome (15 with a mutation, 6 with a microdeletion). With a mean age of 26 years, the most common features were learning disabilities (90%), scoliosis (52%), eye problems (43%), psychiatric issues (30%), and brain imaging anomalies (28%). Learning disabilities were more severe in patients with a microdeletion than in those with a point mutation. From this small study with heterogeneous ascertainment

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we suggest modest adjustments to the general healthcare monitoring of individuals with Sotos syndrome. Although this series includes neoplasia in four cases, this should not be interpreted as incidence. Age-appropriate cancer surveillance should be maintained. © 2011 Wiley-Liss, Inc.

Key words: adults with genetic disorders; familial gigantism; overgrowth syndrome; *NSD1*; Sotos syndrome; transitional care

INTRODUCTION

In the 47 years since Sotos et al. [1964] reported five children at the Massachusetts General Hospital with a distinctive overgrowth syndrome, more than 400 cases of Sotos syndrome have been reported [Baujat and Cormier-Daire, 2007; Tatton-Brown et al., 2009]. The cardinal features include rapid early growth, advanced bone age, head circumference and height >2 SD above the mean, a typical craniofacial gestalt (macrocephaly, high prominent forehead, sparse frontal hairline, inverted triangular face, pointed chin), and learning disabilities ranging from mild to severe [Allanson and Cole, 1996; Cole, 2005; Tatton-Brown et al., 2009]. Although these features have been well-described throughout childhood, little is known about the identification, clinical manifestations and management of individuals diagnosed with Sotos syndrome later in life.

The diagnosis of Sotos syndrome relied solely on clinical criteria until haploinsufficiency of the *NSD1* (nuclear receptor SET domain-containing protein) gene was identified as causative [Kurotaki et al., 2002]. The *NSD1* gene is located at 5q35, the site of a common microdeletion in Japanese patients [Kurotaki et al., 2003], whereas non-Japanese patients are more likely to have a point mutation in *NSD1* [Douglas et al., 2003]. *NSD1* is known to encode a histone methyltransferase involved in chromatin regulation whose epigenetic effects not only cause Sotos syndrome, but may be implicated in sporadic neuroblastoma [Berdasco et al., 2009]. The facial appearance changes with time. Specifically, as the face lengthens the forehead becomes less prominent and the mandible and chin become the dominant facial features [Allanson and Cole, 1996]. This facial gestalt, tall stature, and lack of awareness of the disease among adult medicine physicians makes "possible Marfan syndrome" an occasional referring diagnosis [Maves et al., 2007]. The differential diagnosis of Sotos syndrome in adulthood also includes Weaver syndrome, Simpson–Golabi–Behmel syndrome, and Gorlin syndrome. Caring for adults with genetic syndromes is increasingly recognized as an important part of transitional care and internal medicine but guidelines for screening and managing individuals with Sotos syndrome are not available [Cole, 2005].

We report on a 63-year-old woman who may be the oldest person with molecular confirmation of Sotos syndrome. In addition to this well-characterized individual, we review clinical findings in previously reported adults and provide information on patients from the Spanish Overgrowth Syndrome Registry. From this review we propose several recommendations for health supervision.

CLINICAL REPORT

A 63-year-old white woman with tall stature was referred by the nephrology service for evaluation of possible Marfan syndrome. The past medical history was provided by the patient's sister, her "guardian" since their mother had severe Alzheimer disease, and their father was living out of state; over the period of this evaluation and manuscript submission: both parents have since died. The patient was the first of four pregnancies delivered by cesarean section and not known to be premature. She was described by her father as "spastic" at birth, referring to contractures. From early childhood she was developmentally delayed and had positional lower extremity deformities (pes planus) for which she wore braces. The patient had "fluid tapped from the brain," which may have been for presumed hydrocephalus since she had a pneumoencephalogram. Medical records refer to a "tumor in her chest" which was later found to be an enlarged thymus. She resided at a private school for persons with learning disabilities, though she was aware they were more disabled than herself. She reports with insight and sadness, that she was considered "retarded" during her childhood.

She eventually completed high school, attended a vocational school for 3 years, and lived with her maternal aunt. In addition to this history from the patient and her sister, the family album (Fig. 1) provided a rich photographic history of a healthy-appearing girl with a distinct facial appearance (large head, thin hair, high forehead, elongated face, prominent chin, wide-spaced eyes), tall stature, and long limbs compared to siblings.

In her third decade of life the patient had a bowel obstruction. Surgery for a poorly defined indication included a hysterectomy and oophorectomy. The patient enjoyed many outdoor activities and lived in Bermuda for 8 years prior to moving to Southern California where she was told that she had features of Marfan syndrome. In her twenties she was diagnosed with anemia and hypertension which led to a diagnosis of renal disease. A renal artery biopsy showed fibromuscular dysplasia at age 24 years, treated with a right renal artery bypass with vein graft at age 30. Subsequent angiography showed a "diminutive left upper pole with fibromuscular dysplasia and patent right renal bypass." She underwent a cholecystectomy at that time as well. The patient transferred care at age 58 for treatment of renal insufficiency, which was viewed as chronic kidney disease, stage V. She underwent a successful deceased donor kidney transplant at age 63 years.

Her tall stature and habitus had been described by others as "marfanoid." Echocardiogram at age 64 showed a normal aortic diameter, no evidence of mitral valve prolapse, and mild aortic insufficiency. When examined in the genetics clinic she was a well-groomed, tall, and thin female who moved slowly. She was quietly engaging, speaking in a soft voice. She appeared older than her chronologic age, frail, with uremia.

Her weight was 64.1 kg (75th centile), height 177.4 cm (>97th centile), upper: lower segment ratio 1.03, BMI 20.4, head circumference 59 cm (>97th centile). She was Fitzpatrick phototype 1 given her red hair, light eyes, fair skin, and history of easily sunburning without the ability to tan. Her skin was extensively photodamaged and significant for several hyperkeratotic erythematous papules and plaques over the dorsum of her hands, neck, and face. Her facial appearance was striking for thin hair, receded frontal

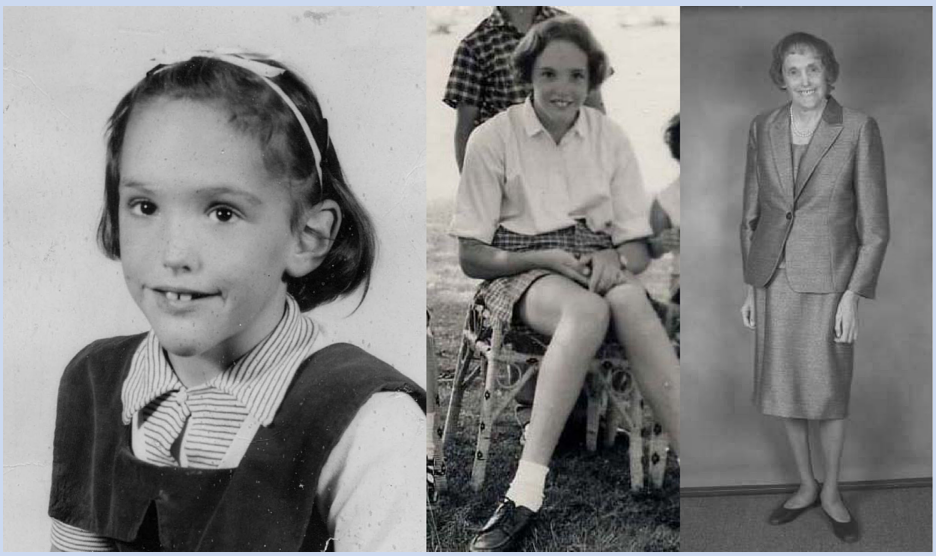

FIG. 1. A photographic natural history of Sotos syndrome shows the patient as a child (specific age unknown), at about 11–12 years, and currently, at 63 years. She has features characteristic of Sotos syndrome including tall stature, typical facial appearance with high forehead and small chin, and those which can be associated with Sotos syndrome and aging, including diffuse contractures and wrinkled skin.

hairline, high forehead with supraorbital prominence, large deep-set eyes, triangular face, malar hypoplasia, small pointed chin, and a small nose and nasal tip. She had mild kyphoscoliosis, long hands and middle fingers without arachnodactyly. There were mild flexible contractures of the fingers, elbows, neck, hips, and knees resulting in a stooped posture. Pes planus was present. She had reduced facial expression. She was oriented, conversant, and had a reasonable fund of knowledge and dry sense of humor.

At age 62 years, a dermatologist diagnosed multiple basal cell and squamous cell carcinomas and many actinic keratoses. Examination of the eyes did not show ectopia lentis. Chromosome analysis showed a 46, XX complement and plasma homocysteine level was normal. Because of the compelling photographs from childhood and characteristic physical findings, Sotos syndrome was considered a likely diagnosis. Subsequent *NSD1* analysis performed at the University of Chicago detected a change at IVS9 + 3_ + 6delGAGT. The same mutation has been seen in two other patients with Sotos syndrome [Tatton-Brown et al., 2005]. Also detected was a known polymorphism, c.6903G>C, which does not lead to an amino acid change (Gly2301Gly) [Douglas et al., 2003].

Neuropsychological testing was performed, and information was gathered from the patient and her primary caregiver. We evaluated for depression, anxiety and ADHD diagnoses using the BDI, BAI, and Connor's Rating Scales, respectively. She did not meet diagnostic criteria for these disorders. Her intellectual functioning fell within the borderline range with a full-scale IQ of 78 (7th centile) on the WAIS-III. The patient's strengths were in verbal comprehension and behavioral regulation with scores in the average range. Areas of weakness include working memory, interpretation of nonverbal information and processing speed. The patient performed better at visuospatial and some working memory tasks upon untimed testing, due to her slow processing speed (1st centile on the processing speed index, WAIS-III). Tests of executive functioning revealed mild deficits, primarily in the areas of organization and initiation. Adaptive behavior skills were below expectations for her chronological age but not a significant deficit.

MATERIALS AND METHODS

Medline searches, limited to English language, were completed using the terms "Sotos syndrome," "cerebral gigantism," and "adults and genetic disease," and reviewed for adult (18 years and older) patients.

The Spanish Overgrowth Syndrome Registry (IRB number CEIC-HULP PI446), was established in 2003 as a national registry with all regions in Spain participating. At present, 236 of 1,500 total entries in its database refer to "Sotos syndrome," with confirmation by clinical information, pictures and molecular tests for *NSD1* in approximately half (n = 112). Sixteen of 112 (14%) individuals were older than 18 years (one patient died at age 38 years).

RESULTS

Combining this new patient, 15 Spanish Overgrowth Registry patients and 11 literature cases [Halal, 1982; Cole et al., 1992; Koenekoop et al., 1995; Inoue et al., 2000; Yen et al., 2000; Cefle et al., 2002; Compton et al., 2004; Tatton-Brown et al., 2005; Martinez-Glez and Lapunzina, 2007; Zechner et al., 2009], there were a total of 27 adults who met clinical diagnostic criteria for Sotos syndrome. Twenty-one of 27 patients (78%) had *NSD1* molecular confirmation (Table I). There were more males than females (1.6:1) and the mean age was 26 years (range 18–63). A "classic" presentation, with at least three of the following

TABLE I. Clinical and Molecular Characteristics of 21 *NSD1* Positive Adults With Sotos Syndrome (New Patient 1, Literature 5, Spanish Overgrowth Syndrome Registry 15)*

	Pathogenic change			Personal characteristics			Neurocognitive features			Clinical features			
Pt identification	Nucleotide change	Amino acid change	Micro-deletion 5q35	Sex	Age (years)	Sotos score[a]	CT/MRI findings	Learning disability	Psychiatric diagnosis	Eye problems	Renal disease	Scoliosis	Tumors
Present case	IVS9+3_+6delGAGT			F	63	1–2–3	VM thin corpus callosum	+ Mild	Social isolation	Cataract 63 years	ESRD due to FMD. Deceased donor transplant	+ Kyphoscoliosis	BCC, SCC
Zechner et al. [2009]	c.6523T>A	C2175S		F	44	1–2–3		"Slow" completed HS					
A. Fryer in Martinez-Glez and Lapunzina [2007]	2493de G exon 5			M	30	1–2–3		+				+	ALL
Cole et al. [1992]	[b]			F	22	1–2–3–4		+		–			Small cell lung carcinoma
Study ID 709	c. 6660 5G>T	C2202S		F	63	1–3		Very mild	Depression			+	
Study ID 197	C6442delAGCGACCA	K2151fs		M	31	1–4		–	–	Myopia, cataracts, retinal detachment	Nephrolithiasis		
Study ID 55	c.2239insT	T747fs		M	22	1–2–3–4	CSV	Mild	Altered sociability	Strabismus		+	
Study ID 56	c.1318C>T	R440X		M	20	1–3–4		IQ 53	–	–		+	
Study ID 140	2386del AAAG	E796fs		M	18	1–2–3–4		IQ 70	–	–		+	
Study ID 166	c.5738A>G	N1913S		M		1–3–4	VM, CSV, left hemisphere atrophy	Moderate	Hyperactivity	–			
Study ID 583	c.4034insT	E1346fs		M	18	1–2–3–4		Moderate		–			
Study ID 54	c.4151insA			M	21	1–2–3–4	Cavum septum pellucidum	IQ 52	Panic disorder	Strabismus, myopia		+	
Study ID 165	c.3680T>G	L1227X		M	24							+	
Study ID 233	c.3091C>T	R1031X		F	18	1–2–3		Moderate dyslexia				+	
Study ID 254	c.3546delCT	S1183fs		F	27	1–3	VM	IQ 63		Strabismus			
Tatton-Brown et al. [2005]			+	NS	20	1–3		"+++"		NS		+	
Tatton-Brown et al. [2005]			+	NS	24	1–3–4		"+++"		NS			
Study ID 606			+	F	19	2–3		Mild		Strabismus, cataract, retinoblastoma			Retinoblastoma[c]
Study ID 40			+	M	28	1–2–3–4		Severe	Depression, agoraphobia	Strabismus	Left renal agenesis	+	
Study ID 263			+	F	20	1–3–4		Severe	Hyperactivity	Proptosis			
Study ID 368			+	M	18	1–2–3–4	Brain atrophy	Severe		Myopia, strabismus			
Total, N (%)	15/21 (71)		6/21 (28)	M 11/19 (58)	Mean 26.2	3 or more 15/21 (71)	6/21 (28)	19/21 (90)	7/21 (30)	9/21 (43)	3/21 (14)	11/21 (52)	4/21 (19)

ALL, acute lymphoblastic leukemia; BCC, basal cell carcinoma; CSV, cavum septum vergae; ESRD, end stage renal disease; F, female; FMD, fibromuscular dysplasia; HS, high school; IQ, intelligence quotient; M, male; NS, not specified; SCC, squamous cell carcinoma; VM, ventriculomegaly.

*Adapted from Baujat et al. [2005].

[a]Sotos score: (1) Characteristic craniofacial appearance/macrocephaly (2) overgrowth (3) learning disabilities (4) advanced bone age.

[b]Point mutation confirmed, nucleotide change not specified, personal correspondence with Trevor Cole, October 19, 2008.

[c]Martinez-Glez and Lapunzina [2007].

characteristics: macrocephaly, tall stature, learning disabilities, advanced bone age and characteristic craniofacial appearance, was present in 70%.

Growth and Development

The data on growth and development was incomplete and used inconsistent units of measure, however, most of the measurements were obtained in adulthood. In 18/21 (86%) cases the head circumferences were >97th centile. The average male height was 182 cm (75th centile) and the average female height was 174 cm (97th centile). As expected, learning disabilities occurred in most patients, ranging from mild to severe. Formal psychometric testing to define the degree of cognitive limitation was not available for all patients.

Craniofacial

Photographs were available for most cases (5/21, 24% had serial photos) and were reviewed by M.R.F., P.L., and A.E.L. to verify the facial appearance of Sotos syndrome. Seven patients met all four cardinal criteria as previously described [Cole and Hughes, 1994]. Formal anthropometric analysis of these non-standardized images was not possible, but limited qualitative analysis noted that the chin became less prominent while the malar hypoplasia and prominent forehead with receded hairline persisted (Fig. 2).

Neuropsychiatric

Neuroimaging in 28% of patients showed midline changes including cavum septum vergae and ventriculomegaly; two were reported to have cerebral atrophy. Seizures were rare (2/21, 9%). A psychiatric diagnosis was reported in 30%, including affective disorders (depression and anxiety) (2), hyperactivity (2), social isolation (2), and anxiety (1). One patient reported in the psychiatric literature [Compton et al., 2004] presented with psychosis.

Tumors

Three adults from the literature had cancer, including retinoblastoma (*RB1* negative) [Martinez-Glez and Lapunzina, 2007], small cell carcinoma [Cole et al., 1992], and acute lymphoblastic leukemia [Fryer, personal communication]. Our patient had numerous non-melanoma skin cancers and pre-cancers, with unclear age of onset, but in approximately the sixth decade. The skin cancers were excised without complication and the actinic keratoses were treated with cryotherapy. The formation of these lesions was attributed to her fair skin and history of extensive sun exposure.

Other Problems

Various congenital and acquired ocular anomalies and vision problems occurred in almost half of the adults with Sotos syndrome, most commonly strabismus, and myopia. Three cases from the ophthalmology literature [Koenekoop et al., 1995; Inoue et al., 2000; Yen et al., 2000] reported more severe abnormalities including glaucoma, bilateral nuclear cataracts, optic disk pallor, retinal atrophy, megalocornea, and megalophthalmos, but the lack of strong clinical description or molecular confirmation of Sotos syndrome makes the significance of these observations uncertain.

Musculoskeletal problems included scoliosis in 52%, in which the severity was not consistently reported, and pes planus in two patients. Three genotyped patients had variable renal anomalies (unilateral renal agenesis, nephrolithiasis, and fibromuscular dysplasia) and one additional clinically diagnosed patient had autosomal dominant polycystic kidney disease [Cefle et al., 2002]. Endocrine, pulmonary, and cardiovascular problems were uncommon, occurring in fewer than three subjects each.

Genotype/Phenotype Correlations

Twenty-one subjects (one new patient, 15 from the Spanish Overgrowth Syndrome Registry, and 5 literature cases) had molecular diagnostic information, there were 15 point mutations and 6 microdeletions. The average age was 26.2 years and most were males (58%). Ninety five percent (20/21) met at least two cardinal criteria in addition to having a pathogenic *NSD1* alteration. Similar medical conditions were noted in both the genotyped cohort and in the entire sample (data not shown). However, Sotos syndrome patients with a microdeletion reported more severe learning disabilities than those with a point mutation.

FIG. 2. Serial photographs of a Spanish male with Sotos syndrome. Note that the chin becomes less prominent, while the high forehead with a receded hairline and the malar hypoplasia persist.

DISCUSSION

This woman in her 7th decade appears to be the oldest known person with Sotos syndrome, adding valuable information regarding the natural history of this syndrome. We make several cautious observations about the clinical phenotype, acknowledging that this is a case report, with a cross-sectional physician-reported survey and modest literature reports.

Although behavioral problems are well-characterized in childhood [Rutter and Cole, 1991], less is known about psychiatric disorders in adults with Sotos syndrome [Cole, 2005]. Further studies are needed to verify the incidence and define the types of these disorders. Some adults with Sotos syndrome have been noted to be "socially isolated" [Cole, 2005 who noted limited data] due to social difficulties, medical illness, physical differences, or autism [Morrow et al., 1990; Buxbaum et al., 2007]. Further confounding may have resulted from misclassification as "retarded." These factors may predispose adults to the reported social difficulties of withdrawal or withdrawing and isolating personality styles [Tantum et al., 1990]. Our patient typifies several of these issues, whose intelligence and dry wit were acknowledged by medical staff. Indeed, her social life is limited to her close family members.

We noted similar midline brain abnormalities as reported by Schaefer et al. [1997] and Horikoshi and Kato [2006]. Future research should emphasize possible correlation of neuroimaging findings with psychiatric disorders.

The only genotype–phenotype correlation noted in this study was that adults with microdeletions have more severe learning disabilities than those with point mutations, as described previously [Tatton-Brown et al., 2005]. Similar genotype–phenotype correlations are seen in the psychological profiles of affected children: Those with *NSD1* point mutations show fewer behavior problems, an easier temperament, and fewer internalizing behaviors [de Boer et al., 2006]. Our review did not have access to details regarding educational or vocational status. A previous telephone interview survey of adults in the Sotos Syndrome Support Association found that these individuals are often described as "socially isolated" [Anderson and Schaefer, 2000]. Although most patients in this study were employed at least part-time, 63% (10/16) lived with their parents and 31% (5/16) had significant psychiatric illness [Anderson and Schaefer, 2000].

Two patients in the Spanish Registry have presumably unrelated renal anomalies, that is, unilateral renal agenesis which may be due to an early embryonic defect, and nephrolithiasis which is usually metabolic in origin. Our new patient has fibromuscular dysplasia, which is viewed as a vascular anomaly rather than intrinsic renal disease. In an additional clinically diagnosed patient, autosomal dominant polycystic kidney disease would be attributed to the known genetic etiology of a mutation in polycystin-1 (*PKD1*, 16p13.3) or polycystin-2 (*PKD2*, 4q21). These disparate diagnoses imply that renal disease is unlikely due to the *NSD1* mutation, but additional cases will be needed to determine if a pattern exists.

The neoplasia risk in Sotos syndrome has been a point of controversy for some time [Cohen, 1999; Tatton-Brown et al., 2009]. The four patients with tumors in this study have varying types of neoplasia, including squamous and basal cell carcinoma, pre B-cell acute lymphoblastic leukemia, small cell lung carcinoma, and retinoblastoma. Our patient has a lifelong history of sun exposure and an age-appropriate onset of cutaneous neoplasms with a high population incidence; therefore, it continues to be difficult to draw any firm conclusions regarding tumor risk in Sotos syndrome.

Guidelines for Adult Health Maintenance

Based on an apparent increased incidence of ophthalmologic disease, we recommend an ophthalmology exam at baseline for all adults with Sotos syndrome. Since nearly half of the subjects had psychiatric disease, regular screening for depression and other common psychiatric disorders is advised. The risk of tumorigenesis remains unclear. In the absence of a predictable timing or pattern of these tumors, a targeted recommendation cannot be made. Paying rigorous attention to age-adjusted cancer screening is necessary. Attention throughout life should be given to postural scoliosis and contractures, since this appears to persist into adulthood.

LIMITATIONS AND STRENGTHS

This study is an initial survey of adults with Sotos syndrome. We attempted to interpret the information derived from the literature cases, acknowledging the inherent bias. Patients from the Spanish Overgrowth Syndrome Registry were reported by individual physicians, and they represent one ethnic group, and data may not be generalizable to all patients with Sotos syndrome. We could not distinguish between congenital and acquired diseases in psychiatric conditions, scoliosis, and neuroimaging findings, which is important for adult healthcare. Although the characterization of our single well-described patient cannot be used as a guideline for all patients with this syndrome, this patient offers a positive glimpse into many aspects of the lifes of older individuals.

CONCLUSIONS

The transition of children with complex diseases to adult healthcare is an important part of adult medicine. Older patients with Sotos syndrome have a distinctive appearance, neuropsychological issues, musculoskeletal features, and a variety of medical problems, but the rarity of the condition and the lack of information about the adult phenotype may represent a challenge to practitioners. We hope this report provides the foundation for larger, prospective studies.

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