Twenty-year follow-up of the facial phenotype of Brazilian patients with Sotos syndrome

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Abstract
Sotos syndrome is characterized by overgrowth starting before birth through childhood with intellectual disability and craniofacial anomalies. The majority of patients are large for gestational age with developmental delay or intellectual disability. The majority of cases are caused by pathogenic variants in NSD1. The most consistent physical features in this disorder are facial dysmorphism including prominent forehead, downslanted palpebral fissures, prognathism with a pointed chin, and a long and narrow face. We present a follow-up to a cohort of 11 individuals found to harbor heterozygous, pathogenic, or likely pathogenic variants in NSD1. We analyzed the facial dysmorphisms and the condition using retrospective over 20 years. Among these patients, followed in our medical genetics outpatient clinic for variable periods of time, all had a phenotype compatible with the characteristic Sotos syndrome facial features, which evolved with time and became superimposed with natural aging modifications. We present here a long-term follow-up of facial features of Brazilian patients with molecularly confirmed Sotos syndrome. In this largest Brazilian cohort of molecularly confirmed patients with Sotos syndrome to date, we provide a careful description of the facial phenotype, which becomes less pronounced with aging and possibly more difficult to recognize in adults. These results may have broad clinical implications for diagnosis and add to the global clinical delineation of this condition.

KEYWORDS
DNA mutational analysis, facial dysmorphism, gigantism, NSD1, Sotos syndrome

1 INTRODUCTION

Sotos syndrome is an overgrowth condition with an autosomal dominant inheritance pattern, caused by haploinsufficiency of NSD1 or, less commonly, NFIX, and estimated to occur in 1:14,000 live births (Tatton-Brown et al., 2005).

First described in 1964 in a cohort of five children with rapid growth, acromegalic features, and nonprogressive intellectual disability (Sotos et al., 1964), now several hundred cases have been reported since that initial description (Baujat & Cormier-Daire, 2007; Tatton-Brown et al., 2005; Tatton-Brown et al., 2020), and the phenotypes of affected children and adults...
are now well characterized (Allanson & Cole, 1996; Fickie et al., 2011; Opitz et al., 1998).

The triad of cardinal clinical features is overgrowth, characteristic facial appearance, and learning disabilities, but other major features include orthopedic (advanced bone age, scoliosis, and joint laxity), cardiac (frequently septal defects), renal (vesicoureteral reflux), and neurologic abnormalities (ventricular dilatation and seizures) together with tumor predisposition (sacroccocygeal teratoma, neuroblastoma, presacral ganglioglioma, acute lymphoblastic leukemia, and small-cell lung cancer). Gestational and perinatal complications are common, including maternal preeclampsia, neonatal jaundice, hypotonia, and poor feeding (Tatton-Brown et al., 2020).

We present 11 individuals with molecularly confirmed Sotos syndrome who were followed for a period of up to 20 years (1999–2019), along with careful photographic documentation of the craniofacial phenotypes. Most literature focuses on patients of North American or European origins; however, to our knowledge, there is only one published cohort of Brazilian patients, which included only pediatric patients, with five molecularly confirmed individuals (Vieira et al., 2015). It is our hope that the photographic documentation of the aging craniofacial features we provide will be a valuable addition to the global delineation of Sotos syndrome.

2 | MATERIALS AND METHODS

We reviewed the medical records of 34 Brazilian patients with suspected Sotos syndrome from 1994 to 2019. These patients were examined by a clinical geneticist with experience in dysmorphology and each satisfied the clinical criteria for the diagnosis of Sotos syndrome. Furthermore, all photographs were reviewed by an outside clinical dysmorphologist to confirm the initial descriptions.

3 | RESULTS

3.1 | Molecular findings

Of the initial 34 patients with a clinical diagnosis of Sotos syndrome, 11/34 (32.3%) were found to harbor heterozygous pathogenic or likely pathogenic variants in NSD1 (Table 1) and, therefore, were included in this study. Of the 11 variants in NSD1, 2 were novel and 9 were previously reported pathogenic variants (Ha et al., 2016). Six subjects (S4–S9) were also evaluated by Multiplex Ligation-dependent Probe Amplification (MLPA) studies with negative test results. As of yet, none of the remaining patients have been submitted to more comprehensive genomic testing.

3.2 | The cohort

Among these 11 patients, four are male and seven are female. All were followed in the same medical genetics outpatient clinic for a variable length of time in the last 25 years. Age at first appointment varied from 5 months to 14 years and 3 months (mean 42.3 months,

| Patient ID | Reference | Variant | ACMG 2015 classification (criteria) (Richards et al., 2015) |
|------------|-----------|---------|----------------------------------------------------------|
| S1         | NM_022455 | c.5965C > T.p.(Gln1989*) Pathogenic (PVS1 + PM1 + PM2 + PP3 + PP4 + PP5) |
| S2         | c.6019A > T.p.(Ile2007Phe) Likely Pathogenic (PM1 + PM2 + PM5 + PP3 + PP4 + PP5) |
| S3         | c.2699del.p.(Pro900Leufs*12)* Pathogenic (PVS1 + PM2 + PP4) |
| S4         | c.2954_2955del.p.(Ser985Cysfs*25) Pathogenic (PVS1 + PM2 + PP4 + PP5) |
| S5         | c.6050G > A.p.(Arg2017Gln) Likely pathogenic (PM1 + PM2 + PP3 + PP4 + PP5) |
| S6         | c.5004C > A.p.(Tyr1668*)a Pathogenic (PVS1 + PM2 + PP3 + PP4) |
| S7         | c.5892 + 1G > T Pathogenic (PVS1 + PP4 + PP5) |
| S8         | c.4740del.p.(Lys1580Asnfs*62) Pathogenic (PVS1 + PM1 + PM2 + PP4) |
| S9         | c.5750 T > C.p.(Leu1917Pro) Likely pathogenic (PM1 + PM2 + PP3 + PP4) |
| S10        | c.3004_3005del.p.(Lys1002Glufs*8) Pathogenic (PVS1 + PM2 + PP4 + PP5) |
| S11        | c.1894C > T.p.(Arg632*) Pathogenic (PVS1 + PM2 + PP3 + PP4) |

*aNovel variants.
| Patient ID | S1  | S2    | S3    | S4    | S5    | S6    | S7    | S8    | S9    | S10   | S11   | TOTAL |
|------------|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|
| Age at first appointment | 5 mo | 2 y 6 mo | 1 y 5 mo | 1 y 9 mo | 10 mo | 9 mo | 1 y 6 mo | 8 y | 14 y | ? | ? | Mean 42.3 mo median 18 mo |
| Age at the clinical diagnosis | 5 mo | 2 y 6 mo | 1 y 5 mo | 1 y 9 mo | 2 y 9 mo | 9 mo | 5 y 7 mo | 8 y | 14 y | ? | ? | Mean 49.5 mo median 21 mo |
| Current age | 9 y | 25 y | 8 y | 17 y | 15 y | 12 y | 22 y | 20 y | 29 y | 25 y | 20 y | Mean 18.4 y median 20 y |
| Familial cases | - | - | - | - | - | - | - | - | - | - | - | 0/11 |
| Pregnancy, birth and perinatal complications | | | | | | | | | | | | |
| Maternal age at conception | 31 y | 22 y | 32 y | 31 y | 33 y | 35 y | 31 y | 30 y | 27 y | ? | ? | Mean 30.2 y median 31 y |
| Paternal age at conception | 36 y | 32 y | 34 y | 30 y | 35 y | 43 y | 36 y | 41 y | 36 y | ? | ? | Mean 35.9 y median 36 y |
| Maternal pre-eclampsia | - | - | - | - | - | + | - | - | + | + | ? | ? | 3/9 (33.3%) |
| Delivery | Term | Term | Term | Preterm | Preterm | Term | Term | Term | Term | ? | ? | Term 7/9 (77.8%) |
| Head circumference | ? | 39 cm | 38 cm | 32.8 cm | 27 cm | 38 cm | 36 cm | ? | ? | ? | ? | Macrocephaly 4/6 (66.7%) |
| Large for gestational age | + | - | - | - | - | - | + | + | + | + | - | 5/11 (45.4%) |
| Jaundice | + | - | + | + | - | + | + | + | + | ? | ? | 7/9 (77.8%) |
| Hypotonia | + | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| Poor feeding | + | - | + | - | - | - | - | - | - | - | ? | ? | 2/9 (22.2%) |
| Respiratory complications | - | - | + | - | + | - | + | - | - | ? | ? | 3/9 (33.3%) |
| Hypoglycemia | - | - | - | + | + | + | - | - | - | - | ? | ? | 2/9 (22.2%) |
| Growth | | | | | | | | | | | | |
| Excessive growth velocity | + | + | + | + | + | - | + | + | + | + | + | 10/11 (90.9%) |
| Advanced bone age | + | - | + | + | + | - | + | + | + | - | - | 7/11 (63.6%) |
| Normal adult height | NA | + | NA | + | NA | NA | - | + | + | + | - | 6/7 (85.7%) |
| Craniofacial features | | | | | | | | | | | | |
| Macrocephaly | + | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| Dolichocephaly | + | + | + | + | + | - | + | + | + | + | + | 10/11 (90.9%) |
| Prominent forehead | + | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| Widely spaced eyes | + | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| Patient ID | TOTAL |
|-----------|-------|
| S1 | S2 | S3 | S4 | S5 | S6 | S7 | S8 | S9 | S10 | S11 | 11/11 (100%) |
| Downsloped palpebral fissures | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| High arched palate | + | ? | + | + | + | + | + | + | - | - | 9/10 (90%) |
| Pointed chin (prognathism) | + | + | + | + | + | + | + | + | + | - | 11/11 (100%) |
| Neurologic and performance | | | | | | | | | | | |
| Intellectual disability | + | + | NA | + | + | + | + | + | + | + | NA | NA | 8/8 (100%) |
| Motor developmental delay | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| Speech delay | + | + | + | + | + | + | + | + | - | - | + | + | 10/11 (90.9%) |
| University enrollment | - | - | - | - | - | - | - | - | - | - | NA | NA | 1/9 (11.1%) |
| Emotional immaturity | - | ? | ? | - | - | - | - | - | - | - | NA | NA | 7/8 (87.5%) |
| Poor Motor Delay | - | + | + | ? | ? | + | - | + | + | - | - | - | 5/9 (55.6%) |
| Abnormal brain imaging | + | NA | + | - | + | + | + | + | + | + | NA | 7/9 (77.8%) |
| Seizures | - | - | - | + | - | - | - | - | - | - | + | 2/11 (18.2%) |
| Musculoskeletal findings | | | | | | | | | | | | | |
| Scoliosis | + | + | + | + | - | + | + | - | + | - | - | - | 7/11 (63.6%) |
| Large hands and feet | + | + | + | + | + | + | + | + | + | + | 11/11 (100%) |
| Hyperlaxity/pes planus | - | - | + | - | + | + | + | + | + | + | 6/11 (54.5%) |
| Other organ anomalies | | | | | | | | | | | | | |
| Renal anomalies | - | - | + | + | + | - | + | - | - | - | 4/11 (36.4%) |
| Cardiac anomalies | - | + | + | + | + | - | + | - | - | - | 6/11 (54.5%) |

Abbreviation: NA, not applicable.
median 18 months). Seven of them are adults, and none have had children. None of them have affected parents (Table 2).

For 10 individuals (90.9%), the main diagnostic hypothesis after the first evaluation was Sotos syndrome. All patients had the classic clinical presentation of overgrowth (tall stature and/or macrocephaly), learning disabilities, and characteristic craniofacial features.

### 3.3 Pregnancy, birth, and perinatal complications

At conception, the mean maternal and paternal age was approximately 30 and 36 years, respectively. One of our patients was born from a consanguineous couple (first cousins). There were no other similarly affected individuals in this family.

Among the nine mothers for whom gestational data is available, three (33.4%) developed hypertension at some point during the pregnancy. The pregnancies were otherwise unremarkable except for one case of gestational diabetes mellitus. Two individuals lacked data regarding gestational age at birth. Among the other nine patients, two (22.2%) were not able to reach full term, one of those being a dizygotic twin. Ten individuals (90.9%) were delivered through cesarean section.

Affected patients are often large for gestational age, and, indeed, the birth length of term pregnancies varied from 48 to 54 cm (mean 52.1 cm, median 53 cm), from the 29th to >99th percentile. Birth weight of term pregnancies varied from 3100 to 4635 g (mean 3892 g, median 3830 g), from the 45th to >99th percentile. Six patients were reported to be large for gestational age.

**FIGURE 1** Serial photographs of four patients depicting the evolution of the facial phenotype: the pointed chin becomes square, the forehead and ocular hypertelorism become less prominent and the jaw line, less narrow. (1) Patient S6 frontal and profile views at 9 months (1A and 1B), 8 years (y) (1C and 1D) and 11 y (1E and 1F). (2) Patient S8 at 8 y (2A and 2B), 17 y (2C and 2D) and 20 y (2E and 2F). (3) Patient S7 at 7 y (3A and 3B), 14 y (3C and 3D) and 18 y (3E and 3F). (4) Patient S4 at 1 y 9 mo (4A and 4B), 11 y (4C and 4D) and 18 y (4E and 4F).
All individuals were hypotonic at birth. Three patients (27.27%) had respiratory problems and two (18.2%) had feeding difficulties. None required tube feeding. These data as well as other major malformations found in the patients are summarized in Table 2.

3.4 Craniofacial features

Serial photographs of nine patients were available. All these individuals had a phenotype compatible with the characteristic facial features of Sotos syndrome, including prominent forehead, prognathism with a pointed chin, downsloping palpebral fissures, and widely spaced eyes; these features evolved with time and became superimposed with natural aging modifications to the facial phenotype (Figure 1). Ten out of 11 patients (90.9%) had macrodolichocephaly and 9/10 (90%) had high arched palates. None had premature tooth eruption (Table 2).

3.5 Growth

The data on growth varied by participant. Eight of the 11 patients had at least seven or more sets of anthropometric measurements at different appointments. One had two sets of measurements and the remaining two had written documentation of excessive growth velocity. Seven patients (63.6%) had advanced bone age. Data on growth are summarized in Table 2. None of our patients developed benign or malignant tumors of any type during the duration of the study.

3.6 Cognitive development

All patients had developmental delay or intellectual disability, with speech delay present in 10/11 patients (92.3%). Among 7 patients for whom data about school performance after the age of 10 was available, 5 (71.4%) were enrolled in special schools or inclusion projects for children with learning disabilities. One of the two remaining patients was enrolled in regular school; however, she had a history of learning difficulties and needed extra credits to achieve passing marks. One of the patients discontinued follow-up at the age of 2 years, before we could accurately assess school performance. One of the patients, at 9 years old, is enrolled in regular school; however, she has problems with mathematics. She is also reported to have juvenile behavior and difficulties socializing with other children.

Among the seven adult patients, two did not complete school, although one of them was later enrolled in an adult education program. Only one patient in our cohort finished high school and went on to pursue further studies. This patient is currently enrolled in a mechatronics technical course at a private university; however, he did have a long history of learning difficulties when he was younger. Data on performance and development are summarized in Table 2.

4 DISCUSSION

Our patients followed the expected clinical courses and natural history of Sotos syndrome in other populations (Cole & Hughes, 1994). The majority (90.9%) were clinically diagnosed with Sotos at their first appointment in our Medical Genetics outpatient clinic, which suggests how highly sensitive the clinical diagnosis by an experienced dysmorphologist can be for this condition.

Facial gestalt has been reported as the most consistent criteria for a clinical diagnosis of Sotos syndrome (Tatton-Brown et al., 2005). While most of the published literature describes patients of Caucasian ethnicity, either North American or European in origin, we provide a detailed study of the facial phenotype of patients from Brazil, a country whose population is highly mixed.

We have made a careful documentation of the facial phenotype (Table 2, Figure 1), including the evolution of facial features over several years. All the patients had macrocephaly, prominent forehead, widely spaced eyes, downsloping palpebral fissures, and prognathism with a pointed chin at the first evaluation. Therefore, even in patients from an ethnic background other than Caucasian, the clinical recognition and suspicion of Sotos syndrome was still possible due to the consistency of the facial dysmorphisms in infancy.

Clinical follow-up, however, evidenced that some facial characteristics change with time, becoming superimposed with normal aging features, as evidenced in Figure 1. The pointed chin, present at infancy and childhood, becomes square, consistent with a finding that was previously reported in adult individuals with Sotos syndrome (Foster et al., 2019). Besides that, the forehead becomes less prominent, the widely spaced eyes less evident and the jaw line less narrow. This suggests a powerful compensatory mechanism that eventually obscures the facial dysmorphism with aging. Therefore, the facial findings typical of Sotos syndrome seem to become less pronounced with aging, which could possibly make the clinical recognition more difficult even for experienced dysmorphologists.

Cognitive impairment is a well-established feature of Sotos syndrome and learning disabilities can vary from mild to severe. Indeed, all our patients presented with mild to moderate learning disabilities, with wide variability of presentation. Most required special education, and two of them left the school system altogether. Only one patient went on to technical school after graduating high school. This suggests the importance of an individualized evaluation and approach to the educational needs of these individuals.

In addition to the three cardinal features, several other clinical characteristics have been outlined as major features of Sotos syndrome. A number of complications have been described in adult patients with Sotos syndrome, including psychiatric, ophthalmological, nephrological, and cardiac complications (Tatton-Brown et al., 2020). Comparing our patients with previously published cohorts (Fickie et al., 2011; Foster et al., 2019; Tatton-Brown et al., 2005) of adult patients, there was no substantial difference in clinical findings.

There is a documented increased risk for neoplasia in Sotos syndrome; however, only a minority of individuals have developed tumors (Tatton-Brown et al., 2020). The spectrum of tumor types
reported is broad (Al-Mulla et al., 2004; Deardorff et al., 2004; Kato et al., 2009; Lapunzina, 2005), and it differs from other overgrowth syndromes. Interestingly, none of our patients presented with or developed any benign or malignant tumors during the duration of the study. We acknowledge, however, that this is a small cohort, and the value of this information is limited.

There is only one established genotype–phenotype correlation in Sotos syndrome: patients with copy number variations in NSD1 have less overgrowth and more pronounced learning disabilities (de Boer et al., 2004; Nagai et al., 2003). All our patients had point mutations; therefore, we could not observe this correlation. Moreover, patients with negative results from NSD1 sequencing were not evaluated through other techniques, such as exome sequencing or chromosomal microarray, which could lead to the diagnosis of other conditions with a clinical overlap to Sotos syndrome.

5 CONCLUSION

To our knowledge, this is the largest Brazilian cohort of molecularly confirmed patients with Sotos syndrome so far. By a careful examination of the craniofacial phenotype, we documented the gradual and moderate change of facial phenotype, which becomes less pronounced with aging and possibly more difficult to recognize in adults. Thus, physicians must have a higher level of suspicion for this condition in adults.

We hope this will be a valuable contribution to the global clinical delineation of Sotos syndrome, especially considering that Brazil has a diverse and mixed population of different ethnic origins, in a context of few descriptions of individuals with Sotos syndrome from diverse populations in the literature.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Matheus Augusto Araújo Castro and Juliana Heather Vedovato dos Santos wrote the first version of the manuscript. Rachel Sayuri Honjo, Guilherme Lopes Yamamoto, and Débora Romeo Bertola performed clinical follow-up of patients and revised the manuscript. Anna C. Hurst reviewed all photographs and revised the manuscript. Lynn P. Chorich and Lawrence C. Layman performed the sequencing and revised the manuscript. Chong Ae Kim wrote and revised the manuscript. Hyung-Goo Kim performed molecular analysis and revised the manuscript.

INFORMED CONSENT STATEMENT

Written informed consent forms were obtained from all involved patients.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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