

# Syndromic craniosynostosis: neuropsycholinguistic abilities and imaging analysis of the central nervous system

Craniossinostoses sindrômicas: habilidades neuropsicolinguísticas e análise por imagem do sistema nervoso central

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## ABSTRACT

**Objective:** To characterize patients with syndromic craniosynostosis with respect to their neuropsycholinguistic abilities and to present these findings together with the brain abnormalities. **Methods:** Eighteen patients with a diagnosis of syndromic craniosynostosis were studied. Eight patients had Apert syndrome and 10 had Crouzon syndrome. They were submitted to phonological evaluation, neuropsychological evaluation and magnetic resonance imaging of the brain. The phonological evaluation was done by behavioral observation of the language, the Peabody test, Token test and a school achievement test. The neuropsychological evaluation included the WISC III and WAIS tests. **Results:** Abnormalities in language abilities were observed and the school achievement test showed abnormalities in 66.67% of the patients. A normal intelligence quotient was observed in 39.3% of the patients, and congenital abnormalities of the central nervous system were observed in 46.4% of the patients. **Conclusion:** Abnormalities of language abilities were observed in the majority of patients with syndromic craniosynostosis, and low cognitive performance was also observed.

**Keywords:** acrocephalosyndactylia; craniofacial dysostosis; central nervous system; neuropsychology; language.

## RESUMO

**Objetivo:** Caracterizar as habilidades neuropsicolinguísticas de indivíduos com craniossinostoses sindrômicas e apresentar esses achados com as anomalias do sistema nervoso central. **Métodos:** Participaram do estudo 18 sujeitos com diagnóstico clínico de craniossinostose sindrômica, 44,4% com a síndrome de Apert e 55,6% síndrome de Crouzon. Todos os sujeitos foram submetidos a avaliação fonoaudiológica, psicológica e exames de ressonância magnética do encéfalo. A avaliação fonoaudiológica foi contemplada pela Observação Comportamental da Linguagem, Teste Peabody (TVIP), Teste Token e Teste de Desempenho Escolar (TDE); enquanto a psicológica utilizou a WISC-III e a WAIS. **Resultados:** Observou-se alteração nas habilidades de linguagem em todos os protocolos utilizados, sendo o TDE o que apresentou maior porcentagem de alteração (66,67%). A avaliação cognitiva evidenciou quociente de inteligência dentro da média em 39,3% dos sujeitos, enquanto que 46,4% apresentaram malformações congênitas do sistema nervoso central. **Conclusão:** Constatou-se alterações nas habilidades de linguagem na maioria dos sujeitos com craniossinostoses sindrômicas, bem como o baixo desempenho cognitivo.

**Palavras-chave:** acrocefalossindactilia; disostose craniofacial; sistema nervoso central; neuropsicologia; linguagem.

Within the field of craniofacial anomalies, there is a heterogeneous group of disorders represented by craniosynostoses, which occur due to premature fusion of one or more cranial sutures and may cause esthetic and functional damage<sup>1</sup>. With a prevalence of one in each 2,500 live births, the craniosynostosis may occur both as isolated disorders or as part of

syndromes. Most syndromic craniosynostosis have autosomal dominant inheritance<sup>2</sup>, which highlights the importance of genetic counseling for these patients.

The most frequent syndromic craniosynostosis include Crouzon, Apert, Saethre-Chotzen, Pfeiffer and Muenke syndromes; the first three accounting for nearly two thirds of syndromic cases<sup>2</sup>.

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Apert syndrome is a congenital disorder characterized primarily by craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet with a tendency to fusion of bony structures. Most cases are sporadic, but autosomal dominant inheritance has been reported<sup>3</sup>. Crouzon syndrome is an autosomal dominant disorder characterized by craniosynostosis causing secondary alterations of the facial bones and facial structure. Common features include hypertelorism, exophthalmos and external strabismus, parrot-beaked nose, short upper lip, hypoplastic maxilla, and a relative mandibular prognathism<sup>4</sup>.

They share other characteristics beyond craniosynostosis, including cranial base anomalies, abnormal facies, limb anomalies and mutation of the fibroblast growth factor receptor 2 gene<sup>2</sup>. Additionally, there is frequent occurrence of increased intracranial pressure, hydrocephaly, optical atrophy, breathing problems, speech and hearing disorders, obstructive sleep apnea and visual impairment<sup>5,6</sup>.

Surgical treatment may be required, for esthetic reasons and neurological complications<sup>6</sup>. In the treatment of these disorders, craniofacial surgery for cranial decompression performed in the first year of life is fundamental to avoid intracranial hypertension, which may have deleterious effects on the cognitive and linguistic development<sup>7,8</sup>.

Regardless of the type or etiology, among craniofacial anomalies, this group represents a significant array of pathologies that may impair different functions of the central nervous system (CNS) during development of the children<sup>9</sup>. These impairments imply the need for multidisciplinary care, with a varied staff of specialists, including plastic surgeons, neurosurgeons, geneticists, dentists, neurologists, speech-language pathologists, ear, nose and throat doctors, orthopedists, social workers, and others<sup>10</sup>.

Within these complex disorders that affect the craniofacial structures, it is possible to observe anatomical and functional interferences that may cause language delays and/or disorders<sup>11</sup>. The hypothesis of the present study was that, in addition to the cognitive alterations, the language alterations that may also be associated with these conditions may include language or learning disorders. Language impairment presents as deficits in comprehension and change in at least one aspect of language, such as phonology, syntax, semantics, and pragmatics<sup>12</sup>.

Learning disability is a broad term. It is a condition when a child's achievement is substantially below what one might expect for that child. It does not include problems that are primarily the result of intellectual disabilities, emotional disturbance, visual, hearing, or emotional disabilities. These children, despite having an average or above average level of intelligence, have difficulty acquiring basic academic skills, such as the fluent reading of words, correct spelling, written expression and mathematical operations<sup>13</sup>.

Assessment of the linguistic and cognitive integrity by speech-language and psychological evaluations, herein called

neuropsycholinguistic, are fundamental to rule out any language and learning disorders in syndromic craniosynostosis<sup>11,14</sup>.

This study evaluated the neuropsycholinguistic abilities and morphology of the CNS in patients with syndromic craniosynostosis. The aim of this study was to characterize this population with regard to their neuropsycholinguistic aspects and to present these findings together with the brain abnormalities.

## METHODS

### Ethical aspects

This study was conducted from 2008 to 2011 at the Hospital for Rehabilitation of Craniofacial Anomalies of the University of São Paulo, Bauru, São Paulo (a tertiary reference center for craniofacial anomalies), after approval by the Institutional Review Board (n. 288/2006). All criteria of Regulation 196/96 were met. All patients or legal caretakers agreeing to participate in the study signed an informed consent form. All the patients who were evaluated were regularly enrolled at this hospital and met the inclusion criteria.

### Sample

The study was conducted on 18 patients with a clinical diagnosis of syndromic craniosynostosis, with a mean age of 18.75 years (standard deviation 64.38; minimum 6.33 years; maximum 31.25 years). There was predominance of a low socioeconomic level (83.3%), ranging from low to high<sup>15</sup>. The percentage of patients with a diagnosis of syndromic craniosynostosis was 44.4% Apert syndrome (AS) and 55.6% Crouzon syndrome (CS), as described in Table 1.

*Inclusion criteria:* Patients receiving regular treatment at the hospital where the study was conducted; diagnosis of syndromic craniosynostosis; availability to perform all evaluations planned in the study.

*Exclusion criteria:* Hearing impairment: sensorineural or conductive hearing loss.

### Procedures

All patients were submitted to speech-language and psychological analyses and magnetic resonance imaging (MRI) of the brain. It should be highlighted that all analyses were performed according to the chronological age of patients.

**Table 1.** Sample distribution among Apert and Crouzon syndromes, with information on the number of patients and mean age.

Variable	Apert syndrome - 8 patients	Crouzon syndrome - 10 patients
Mean	23 years and 5 months	15 years and 2 months
Standard deviation	54.59 months	46.33 months
Minimum	14 years and 9 months	6 years and 4 months
Maximum	31 years and 3 months	20 years and 9 months

### Auditory and speech analysis

Initially an audiological evaluation was performed, which was a prerequisite for continuation of the other evaluations. This was comprised clinical ear inspection, threshold tone audiometry<sup>16</sup> and tympanometry<sup>17</sup>. All patients were required to have results within the normal range.

The speech-language analysis was performed by behavioral observation of language (qualitative analysis)<sup>18</sup>, as well as utilization of standardized protocols that allowed quantification.

Concerning the behavioral observation of language, the parameters of each specific age range were considered, taking into account language reception and expression. Table 2 shows the details of observation of each language level<sup>19</sup>.

The speech-language analyses performed, the instruments employed, as well as their objectives, composition and parameters for analysis<sup>18,20-22</sup> are shown in Table 3.

### Psychological analysis

The cognitive analysis was obtained using the Wechsler Intelligence Scale for Children – III<sup>23</sup>, a standardized test that measures intellectual functioning in children aged six to 16 years, and the Wechsler Adult Intelligence Scale<sup>24</sup>, a test designed to measure intelligence in adults and older teenagers. The intelligence quotients (IQ) were obtained as verbal IQ, performance IQ and full IQ. The scales have a mean (average) standard score of 100. Scores from 90–110 are considered

average. Just outside of that range is the high average range (110–119), the low average range (80–89), and the borderline range is 70–79. Preschool children were assessed using the form L-M of the Stanford-Binet scale<sup>25</sup>.

A numerical value of 70 was considered to be the dividing line between patients with satisfactory IQ (equal to or greater than 70) and those with unsatisfactory IQ (below 70), as suggested by the World Health Organization<sup>26</sup>. Although the most updated definition of intellectual disability consists of IQ measurement plus an adaptive scale, in this study we adopted the measure of the IQ only, to establish correlations.

### Neuroimaging examination

The MRIs were obtained in a 0.5T scanner (Flexart, TOSHIBA, Japan) in sequences T1, T1 inversion recovery, T2 and Flair, in sagittal, coronal and axial planes, and later evaluated by a neurologist. It is important to explain that as the MRI scans were done at low resolutions (0.5T) it was not feasible to evaluate small malformations such as focal dysplasias.

### Analysis of results

The results were tabulated and scored according to the guidelines and standardization of tests employed for speech-language and cognitive analysis. The Student's t-test, Tukey test, analysis of variance, chi-square test and Spearman's correlation were applied for comparison and correlation between variables.

**Table 2.** Description of behaviors analyzed for each language component in receptive and expressive language<sup>19</sup>.

Language components	Expressive	Receptive
Phonology	Production of speech sounds	Hearing, sound discrimination and processing
Syntax	Utilization of grammatical structures of language	Understanding of grammatical structures of language
Semantics	Utilization of vocabulary, meaning and concept	Understanding of vocabulary, meaning and concept
Pragmatics	Functional utilization of language as communication means, coherent responses, maintenance of topic	Understanding of language

**Table 3.** Instruments employed for evaluation of receptive and expressive aspects of language, presenting the instrument name, objective, composition and parameters.

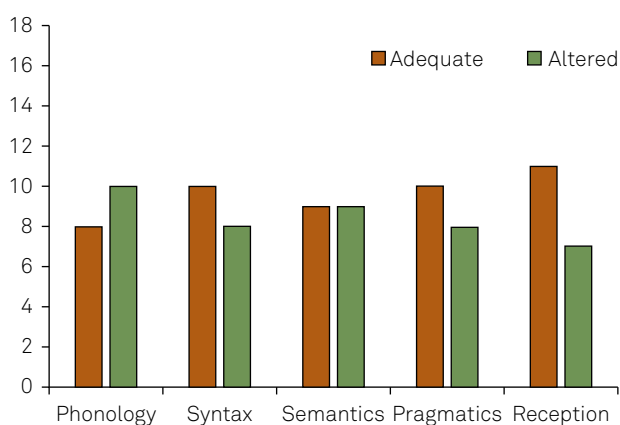
Instrument	Objective	Composition of instrument	Parameters
Behavioral observation of language <sup>18</sup>	Receptive and expressive language	Spontaneous and semi-directed conversation	Observation of communication resources used by the individual Result: adequate or altered
Peabody picture vocabulary test <sup>20</sup>	Lexical development in the receptive domain	The areas included: people, actions, qualities, body parts, time, nature, places, objectives, animals, tools and instruments and mathematical terms	Result: upper high; lower high; upper medium; lower medium; upper low; lower low
School achievement test <sup>21</sup>	Reading, arithmetics and writing	Reading: decoding of 70 isolated words Writing: writing their own name and 34 words presented as dictation Arithmetics: resolution of 35 arithmetic operations, written and orally Performed only on literate individuals	Result: low, medium or high, according to the educational level presented
Token test <sup>22</sup>	Understanding ability at the receptive level	36 commands, gradually increasing the complexity of the test, involving 20 symbols, differentiated by shape, size and color	Gross score, which will be adjusted to the score corrected according to the educational level Result: upper medium, medium, normal, mild difficulty, moderate difficulty, severe difficulty and very severe difficulty

## RESULTS

In the present sample, five patients (27.78%) did not present with impairment of spoken language abilities, of whom four had CS and one had AS. Figure 1 shows the occurrence of disorders for each ability assessed by the behavioral observation of language.

The results of quantitative standardized tests are presented in Table 4. The Peabody Picture Vocabulary Test (PPVT) showed more diffuse distribution of scores, the Token test was altered in 27.78% of patients and the school achievement test revealed low scores for most patients (66.67%).

Considering the findings of the clinical and standardized speech-language evaluation, it was possible to infer the



**Figure.** Performance in oral language abilities observed by the behavioral observation of language.

speech-language diagnostic hypothesis, in which 44.5% of the sample presented with a learning disorder and 16.7% had a language disorder, while 33.4% of the sample did not present with language alterations. One patient had difficulties with written language (Patient 3).

Table 5 shows the intelligence quotient (IQ) results (verbal, performance and full IQs), which revealed IQs within the average in 50% of patients analyzed, and four patients (22.2%) exhibited intellectual disability.

Concerning the CNS disorders, it should be mentioned that encephalomalacia is related to surgical complications, rather than a congenital disorder of the brain. Thus, both congenital and acquired disorders were observed on the MRI, showing that 61.1% of individuals exhibited abnormalities of the CNS (Table 6).

In the statistical analysis of variables, the results indicated a correlation between the IQ and speech-language diagnosis ( $p = 0.002$ ).

The speech-language diagnostic hypothesis revealed an association between the results of the PPVT ( $p = 0.046$ ), Token test ( $p = 0.004$ ) and school achievement test ( $p = 0.001$ ); as well as the diagnosis of language disorder (0.002) and learning disorder (0.021). Thus, it may be inferred that the results obtained by complementary evaluation were sensitive enough to define the hypothesis, confirming the findings (Table 7).

Concerning the morphological alterations of the CNS, the results revealed an association between hypoplasia of the corpus callosum and the findings of the PPVT test ( $p = 0.037$ ), i.e., the performance of the patients.

**Table 4.** Results of standardized tests: PPVT, Token test and school achievement test, according to the classification proposed and score achieved of each patient, specifying age and gender.

Patient	Gender	Years	Syndrome	PPVT		Token test		School achievement test	
				Score	Classification	Score	Classification	Score	Classification
1	M	26y1m	AS	67	Lower low	27.56	Mild difficulty	87	Low
2	F	18y1m	AS	116	Upper medium	34.56	Upper medium	137	Superior
3	M	19y9m	AS	97	Medium	35.56	Medium	121	Low
4	F	25y	AS	113	Upper medium	31.6	Medium	112	Low
5	F	16y1m	AS	47	Lower low	28.32	Mild difficulty	110	Low
6	M	12y1m	AS	72	Upper low	30.54	Medium	85	Low
7	F	18y1m	AS	83	Upper low	30.76	Medium	113	Low
8	F	21y1m	AS	43	Lower low	17.76	Moderate difficulty	70	Low
9	M	16y5m	CS	54	Lower low	17.5	Moderate difficulty	35	Low
10	F	12y	CS	101	Medium	34.46	Upper medium	123	Medium
11	M	17y4m	CS	86	Lower medium	31.06	Medium	126	Medium
12	M	12y8m	CS	87	Lower medium	29.26	Medium	111	Low
13	M	5y3m	CS	58	Lower low	14.46	Severe difficulty	28	Low
14	M	15y3m	CS	106	Upper medium	35.13	Upper medium	95	Low
15	M	12y	CS	88	Medium	31.86	Medium	131	High
16	M	16y3m	CS	85	Lower medium	34.36	Upper medium	124	High
17	M	10y9m	CS	97	Medium	37.46	Upper medium	118	Medium
18	M	8y4m	CS	72	Upper low	28.76	Medium	71	Low

AS: Apert syndrome; CS: Crouzon syndrome; PPVT: Peabody picture vocabulary.

**Table 5.** Description of values of psychological evaluation of the verbal intelligence quotient (VIQ); performance intelligence quotient (PIQ) and full intelligence quotient (FIQ) of patients in the sample.

Patients	Syndrome	TEST	VIQ	PIQ	FIQ	Final classification
1	AS	WAIS	71	74	71	Borderline
2	AS	WISC-III	100	108	104	Average
3	AS	WISC-III	65	71	65	Intellectual disability
4	AS	WAIS	78	68	70	Borderline
5	AS	WISC-III	75	73	72	Borderline
6	AS	Terman-Merril	-	-	84	Average
7	AS	WISC-III	74	86	78	Borderline
8	AS	WISC-III	48	51	47	Intellectual disability
9	CS	WISC-III	48	49	46	Intellectual disability
10	CS	WISC-III	95	93	93	Average
11	CS	WISC-III	80	72	74	Borderline
12	CS	WISC-III	91	98	93	Average
13	CS	WISC-III	57	61	56	Intellectual disability
14	CS	WISC-III	92	95	93	Average
15	CS	WISC-III	101	100	101	Average
16	CS	WISC-III	101	97	98	Average
17	CS	WISC-III	112	90	102	Average
18	CS	WISC-III	72	96	82	Average

(-): not performed; AS: Apert syndrome; CS: Crouzon syndrome; WISC: Wechsler Intelligence Scale for Children; WAIS: Wechsler Adult Intelligence Scale.

**Table 6.** Findings of magnetic resonance imaging of the brain indicating the disorders observed in patients in the sample.

Patients	Neuroimaging findings					
	Ventriculomegaly	Corpus callosum	Septum pellucidum	Arachnoid cyst	Chiari I	Encephalomalacia
1	-	-	-	-	-	-
2	-	-	-	-	-	-
3	-	Hypoplasia	-	-	-	-
4	-	-	Cavum	+	-	-
5	+	Hypoplasia	-	-	-	-
6	-	-	-	-	-	-
7	-	Hypoplasia	Hypoplasia	-	-	-
8	-	-	Hypoplasia	-	-	-
9	-	Hypoplasia	-	-	+	-
10	-	-	-	-	-	+
11	-	-	-	+	-	-
12	-	-	-	-	-	-
13	-	-	-	-	-	-
14	-	-	-	-	-	+
15	-	-	-	-	-	+
16	-	-	-	-	-	-
17	-	-	-	-	-	-
18	+	-	-	-	-	-

(-) absent; (+) present.

## DISCUSSION

Syndromic craniosynostosis, especially AS and CS, are diagnosed by clinical evaluation by geneticists, taking into account the phenotypic aspects, ideally adding a genetic investigation by molecular biology analysis. Our cohort had casual equal distribution of genders, with a predominance of patients with CS (Table 1). No studies were found in the literature indicating the specific occurrence of CS.

Despite the existence of studies attempting to correlate factors that interfere with neuropsychological development in AS and CS, there are few studies in the literature specific to CS, possibly because the intellectual disability in this group is much lower compared to those with AS. Patients with AS presented with mild and irregular intellectual disability, with varied alterations in some brain structures, besides the influence of the socioeconomic level and educational level of the parents<sup>27</sup>. In the present study, the prevalence of intellectual disability in patients with AS was 22.2%.



**Table 7.** Summarized findings of language tests with the respective speech-language diagnoses.

Patients	Syndrome	QI	PPVT	Token test	School achievement test	Speech-Language diagnosis
1	AS	71	Lower low	Mild difficulty	Low	Learning disabilities
2	AS	104	Upper medium	Upper medium	Superior	Normal
3	AS	65	Medium	Medium	Low	Learning disabilities
4	AS	70	Upper medium	Medium	Low	Learning disabilities
5	AS	72	Lower low	Mild difficulty	Low	Learning disabilities
6	AS	84	Upper low	Medium	Low	Learning disabilities
7	AS	78	Upper low	Medium	Low	Learning disabilities
8	AS	47	Lower low	Moderate difficulty	Low	Language impairment
9	CS	46	Lower low	Moderate difficulty	Low	Language impairment
10	CS	93	Medium	Upper medium	Medium	Normal
11	CS	74	Lower medium	Medium	Medium	Normal
12	CS	93	Lower medium	Medium	Low	Learning disabilities
13	CS	56	Lower low	Severe difficulty	Low	Language impairment
14	CS	93	Upper medium	Upper medium	Low	Learning disabilities
15	CS	101	Medium	Medium	High	Normal
16	CS	98	Lower medium	Upper medium	High	Normal
17	CS	102	Medium	Upper medium	Medium	Normal
18	CS	82	Upper low	Medium	Low	Learning disabilities

AS: Apert syndrome; CS: Crouzon syndrome; PPVT: Peabody picture vocabulary test.

The literature reveals the need for more thorough neuropsychological evaluation for patients with AS, considering the heterogeneity of cognitive alterations<sup>28</sup>, as was also observed in this study (Table 3) in the different age ranges. This wide age range implies interferences from the effects of cranial deformities and also from the treatments received.

Congenital malformations of the CNS were observed in 61.1% of patients with syndromic craniosynostosis (Table 4). The literature describes alterations in the MRI of patients with AS of 55.6%<sup>29</sup>, compared to 42.8%<sup>30</sup> and 40%<sup>31</sup> in patients with CS.

This study did not find significant correlation between the MRI findings and the IQ and language abilities (Table 5). It should be highlighted that all patients with AS<sup>27</sup> and CS<sup>30</sup> with normal brain structures exhibited IQs above 70, showing a tendency.

The language abilities were altered in 72.3% of the sample (Figure). This marked difficulty is reported in the literature, indicating problems in both expressive and receptive language<sup>32</sup>, as well as specific alterations in the syntactic level of expressive language<sup>33</sup>.

The standardized instruments that allow quantitative analysis in speech-language pathology do not address all age ranges; therefore, the added use of behavioral observation of language was necessary, so all data could be combined to guide the language diagnosis.

Specifically, 44.44% of patients exhibited an altered performance in the PPVT (Table 2), while the literature indicates alterations in 100% of cases of syndromic craniosynostosis<sup>33</sup>.

Understanding was altered, as indicated by the Token test in 27.78% and 58% in the behavioral observation of language. Corroborating this finding, Shipster et al.<sup>34</sup> found that understanding was altered in 40% of children with AS.

The result of the school achievement test revealed low scores in 12 patients (66.67%), characterizing specific cases of learning disorders (Table 2).

The speech-language analysis allowed characterization of the close interaction between developmental aspects and IQ, hence the utilization of the term neuropsycholinguistic development was pertinent. The patients analyzed showed a relationship between low IQ and language disorders, with smaller global impairment for patients with only learning disorders, as previously reported in the literature in studies on patients with AS<sup>35</sup>, CS<sup>14,31</sup> and Saethre-Chotzen syndrome<sup>9</sup>.

The understanding of language and learning disorders observed in patients with syndromic craniosynostosis, relating to the several factors investigated, allows a better therapeutic approach and contributes to the understanding of neuropsycholinguistic disorders, addressing the parallelism between biological aspects (neuronal connectivity and brain circuits as a whole) and environmental aspects (adequate stimulation by healthy affective and challenging cognitive interactions).

The limitations of the evaluation of speech-language abilities across a wide age range, as in the present study, should be noted. In an attempt to overcome this limitation, the study included behavioral observations of language. Further studies are warranted to follow up and better understand the communication abilities of patients with syndromic craniosynostosis, as well as specific studies for validation of new instruments for assessment.

In conclusion, alterations in language abilities were present in most patients with syndromic craniosynostoses, as well as morphological anomalies of the CNS. Low cognitive performance was observed in a few patients. It should be highlighted that learning disorders were correlated with milder cognitive alterations.

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