Cognitive assessment methods of patients with Apert and Crouzon syndrome

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ABSTRACT

Introduction: Bilateral Coronal Craniosynostosis implies a decrease in the Cranial Perimeter (CP) in the anteroposterior axis (Brachycephaly) and is frequently associated with an increase in the cephalocaudal (vertical height) axis of the skull (Turrycephaly); being one of the most common findings in Crouzon and Apert Syndromes (Syndromic Craniosynostosis). In this Scope Review study, among the Syndromic Craniosynostosis, Apert and Crouzon Syndromes will be of special interest. Objective: This study aimed to identify, analyze, and synthesize the appropriate cognitive assessment methods for monitoring the evolution of patients with syndromic craniosynostosis, in particular Apert's and Crouzon's syndromes. **Method:** This is a scope review. In order to formulate the research guiding question and the searching strategy, the *Population* [((Apert OR Crouzon) AND (Disease OR Syndrom*))], *Concept* [((cognit* OR neurobehavioral OR neurocognit* OR neuropsyc*) AND (evaluation OR evaluations OR assessment OR "test" OR tests OR status OR development OR disorder OR disorders OR impairment OR impairments OR impaired OR function OR functions))] and *Context* (in any context) strategy was used. The articles written in English, Portuguese, and Spanish in any period were included. The search was performed in the following databases: Embase, Scopus, National Library of Medicine (PubMed/MEDLINE), and in the BVS Salud network (PAHO, WHO, BIREME, LILACS). **Results:** many internationally validated cognitive assessment tests were applied to patients with Apert and Crouzon, but no standardization (protocol) was followed. Of the 75 types of Cognitive Tests applied, the Wechsler Intelligence Scale predominated, 50%. In the evaluated population, two age groups predominated: school children and adolescents. Children with Apert and Crouzon had worse scores on disorders of socialization, attention, and internalization when compared to the normative group, with the worst results found in Apert. Factors that interfere with cognitive development: intracranial pressure, brain malformations, genetics, age at surgical correction, institutionalization, family environment, caregiver education, and socioeconomic status. **Conclusion:** the results contributed to a better understanding of the cognitive profile of patients with these syndromes and only by knowing about the neuropsychomotor, cognitive, and psychosocial skills and difficulties of these patients with Apert and Crouzon that health, school, and caregiver teams will be able to understand the perceptive capacity in the learning process of these patients deeply and will be able to offer the most appropriate stimuli at the most opportune time.
Keywords: Apert, Crouzon, Neuropsyc, Tests, Development.

INTRODUCTION

Syndromic craniosynostosis consists of the premature fusion of cranial sutures in syndromic patients and affects approximately 1:100,000 to 1:30,000 live births causing skull growth restriction and skull base changes with associated hypoplasia and dysmorphism[1]. Patients with syndromic craniosynostosis are more likely to have ventricular dilation, hydrocephalus, expansion of the subarachnoid space, and cerebellar tonsillar hernia than patients with sporadic single suture craniosynostosis[1-2]. The cranial morphological changes observed in syndromic craniosynostosis are varied, with more than 150 associated syndromes[1], including Apert and Crouzon syndromes of interest in this study.

The prevalence of **Apert syndrome** ranges from 1:80,000 to 1:160,000 live births[1,3-4]. In Apert syndrome, brachycephalic-type craniosynostosis is observed due to a craniofacial midline closure defect that occurs due to the coalescence of bone islands resulting in midface malformations, dental anomalies, cleft palate or narrow palate with swellings, and syndactyly, in addition to other axial skeletal abnormalities. Most cases of Apert arise sporadically due to mutations in the FGFR2 gene, although there are familial cases with the transmission. Apert syndrome is characterized by the presence of

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multisuture craniosynostosis, midface retrusion, and syndactyly of the hands. Malformations are present at birth, intelligence can be affected and functional deficits will result[5-7] (secondary to nonacquisition of function or loss of already acquired functional capacity), especially abnormalities in the following systems: a) skeletal (progressive synostosis of multiple bones); b) respiratory[1,76]; and c) central and peripheral nervous system, as they directly interfere with cognitive development. Children with Apert have a wide range of cognitive development and IQ scores due to multifactorial causes such as the age of the child at the first cranial surgery performed, white matter anomalies, ventriculomegaly, visual and auditory impairments, deficient fine motor skills due to syndactyly, speech and language development, psychosocial aspects, the environment in which the child develops (family or institution) and others[1,5,61,65,69-73,78]. Children with Apert syndrome raised within the family have better cognitive development than their institutionalized peers[6,8-10]. The influence of white matter abnormalities on cognitive development and IQ score is variable in the literature, and the results of studies of white matter malformations (of the corpus callosum, septum pellucidum, and limbic system) suggest that these malformations may lead to a higher incidence of memory, cognition and behavior disorders[1,6,8-9,11-13]. Anomalies of the septum pellucidum were often associated with an intelligence quotient (IQ) < 70[4,10,13-14]. The literature proposes the following clinical diagnostic classification: a) classic clinical features (multisuture craniosynostosis, midface retrusion, and syndactyly) or b) clinical features suggestive of a heterozygous pathogenic variant in FGFR2 identified by molecular genetic testing[4]. All individuals with Apert have a heterozygous pathogenic variant in FGFR2, and FGFR2 sequence analysis detects small intragenic deletions/insertions, missense, nonsense, and splicing site variants, and two adjacent mutations, named S252 W and P253R. The mutation occurs in the fibroblast growth factor receptor 2 (FGFR2) gene[4,10].

The incidence of **Crouzon syndrome** is variable in the literature, reported to be between 1:50,000 and 1:1,000[1], regardless of involvement according to sex; however, there are reports that sagittal and/or metopic craniosynostosis predominates in males, and when the craniosynostosis is coronal or bicoronal, it predominates in females. Crouzon syndrome is the most frequent craniofacial dysostosis, accounting for approximately 4.8% of all cases of craniosynostosis and being the most common type of complex craniosynostosis. The dominant transmission rate is 100%, and it has large-scale penetrance with highly variable phenotypic expression. Crouzon syndrome is a multifactorial dysgenetic syndrome characterized by brachycephaly, pronounced skull fingerprints, midface hypoplasia, shallow orbits, and alteration of the FGFR2 gene[1,9-10,15-16]. In Crouzon syndrome with acanthosis nigricans, brachycephaly, pronounced skull fingerprints, midface hypoplasia, shallow orbits, and alteration of the FGFR3 gene are observed[1-2,6,9-10,12-13,15, 17-18]. Both the FGFR2 gene and the FGFR3 gene are related to fibroblast growth factors and the extracellular matrix. Mutations in these genes result in changes in the extracellular matrix, which starts to secrete cytokines in an autocrine and paracrine manner, modifying the matrix itself and altering the osteogenic process, resulting in the abnormalities found in Crouzon syndrome[78]. The early fusion of the cranial, centrofacial sutures and the skull base determines brachycephaly, as the fused bones become a single, fixed bone structure; compensatory growth toward the open sutures in an attempt to enable craniofacial growth and brain development results in abnormal bone growth and facial deformities[1,10,15-16]. Crouzon malformations are responsible for the functional deficits (secondary to the nonacquisition of function or to the loss of the functional capacity already acquired), especially the following alterations: a) short upper lip, maxillary hypoplasticity, prognathism, centrofacial hypoplasia, hypoplastic maxilla, dental disocclusion, V-shaped dental arch with widely spaced teeth, cleft palate or lip and palate, high palate, bifid uvula, short upper lip, prominent lower lip and tongue, micrognathia, decreased size of the upper dental arch, crowding of the deciduous dentition and secondary, crossbite, malformed teeth, delayed tooth eruption, impactions, maxillary canine, ectopic tooth eruption, and tooth agenesis; b) conductive hearing loss resulting from middle ear deformities such as stapes alterations, fusion on the promontory, malleus ankylosis, distortions and narrowing of the middle ear diameter, tympanic membrane agenesis and external auditory canal atresia. Recurrent infections of the otitis media type occur due to existing malformations and contribute to hearing loss; c) in the integumentary system, in Crouzon syndrome

with acanthosis nigricans, there are velvety brown to black spots on the neck, armpits and inguinal region; d) in the musculoskeletal system, there is progressive synostosis of multiple bones (skull, face, cervical vertebrae) causing fusion of cervical vertebrae, especially in C2-C3 and C5-C6; e) in the respiratory system, there is a "parrot's beak nose" (Pollybeak deformity) due to marked hypoplasia of the jaws and anterior shortening of the nasal dorsum[1,15,20-23]. Upper airway obstruction is secondary to septal deviation, anterior nasal shortening and rhinopharyngeal narrowing, which causes acute respiratory distress, dyspnea, polypnea, apnea and snoring during sleep. The retrusive maxilla and the high-arched palate lead to respiratory failure of varying degrees and obstructive sleep apnea syndrome (OSAS); e) in the central and peripheral nervous system, there is brachycephaly and pronounced fingerprints of the skull, high and broad forehead, bulging of the anterior fontanelle, occipital flattening and front occipital protuberance (turricephaly). Cognitive development is normal in most cases. There are reports in the literature of patients with cognitive impairment secondary to intracranial hypertension (ICH) of prolonged duration with delayed surgical correction[6,11,15-16,24]. ICH and progressive hydrocephalus can occur in patients with Crouzon and lead to consequences such as cognitive deficits and delays in neuropsychomotor development, making early diagnosis and early management of ICH and hydrocephalus imperative. Jugular stenosis present in patients with Crouzon disease leads to cerebral venous congestion, impaired absorption of cerebrospinal fluid and hydrocephalus. Cerebral venous congestion persists even after ventriculoperitoneal shunt (VPD) surgery for the correction of hydrocephalus, progressing to tonsillar herniation. The development of cerebriform impressions in the cranio-occipital region, ICH and enlargement of the pituitary fossa are warning signs of severity. Brain malformations such as ventriculomegaly, Arnold-Chiari malformation and agenesis of the corpus callosum can be found in Crouzon; f) hypertelorism, exophthalmos, bilateral proptosis, divergent strabismus, optic atrophy, loss of visual acuity, nystagmus, coloboma, anisocoria, micro- or megalocornea, cataract, glaucoma, visual disturbances secondary to paresis or agenesis of the extrinsic ocular muscles. Optic atrophy results from the narrow optic canal. Ocular exposure as a result of shallow orbits may result in corneal abrasions, conjunctivitis, or keratoconjunctivitis. ICH can cause complications such as bilateral optic atrophy, nystagmus, strabismus and blindness.

Cognitive assessment investigates the processes of learning and knowledge acquisition through the perception of information from the environment in which the individual is inserted and which is registered in his or her memory. It investigates the learning process that consists of competencies, skills, knowledge, behaviors and values that have been acquired or modified as a result of study, experience, training, reasoning and observation. The processes and acquisition of knowledge are obtained through perception. Perception is the cerebral function that assigns significance to sensory input based on the history of past experiences (memories). Through perception, an individual organizes and interprets his or her sensory impressions to attribute meaning to his environment. Perception consists of the acquisition, interpretation, selection, and organization of information obtained by the senses, and cognitive evaluation investigates in detail the functional capacity of the individual. The importance of cognitive evaluation is to enable the study of the functional capabilities of the individual through the use of instruments (scales, exams, and tests) that evaluate the performance of the individual concerning language, attention, memory, and reasoning, defining the profile by its strengths and difficulties concerning learning. The relevance of the cognitive assessment in Apert and Crouzon is to provide detailed information on the neuropsychomotor, cognitive, and psychosocial skills and difficulties of these patients, thus contributing to the better ability of teams (health, school, and caregivers) to meet the special needs of these patients, offering stimulation and necessary treatments in the most appropriate manner and at the most opportune time, which will enable these patients to reach their full development and become functionally capable, independent adults with satisfactory quality of life[20,25-32].

The present study aimed to identify, analyze and summarize the appropriate cognitive assessment methods for monitoring the evolution of patients with syndromic craniostenosis, in particular, Apert syndrome and Crouzon syndrome.

METHODOLOGY

This is a scope review that follows the proposal by the Joanna Briggs Institute (JBI, 2021)[33-34].

This review was structured as follows: 1) elaboration of the guiding question and the objective of the review; 2) elaboration of the search strategy; 3) search in databases; 4) selection of articles based on reading titles and abstracts; 5) selection of scientific articles based on their full reading; 6) summary of results; and 7) presentation and discussion of the results found.

To formulate the guiding question of the research and the search strategy, the *Population, Concept and Context* (PCC) strategy was used. Thus, P-patients were defined as having syndromic craniostenosis (Apert and Crouzon syndrome); C-cognitive assessment methods; C-in any context. Following this definition, the following guiding question was elaborated: "What are the cognitive assessment methods used in patients with Syndromic Craniostenosis (Apert and Crouzon syndromes).

Inclusion criteria were articles containing the three elements of the PCC, which answered the research question, written in English, Portuguese, or Spanish at any time. Articles written in other languages, those that did not answer the guiding question of the study, literature reviews, expert opinions, pamphlets, or those without full texts *online* were excluded.

The search for articles was conducted from May 6 to June 8, 2022, with the support of two librarians in the following databases: *Embase, Scopus, National Library of Medicine (PUBMED/MEDLINE) and the VHL Salud network (PAHO, WHO, BIREME, LILACS)*.

Health descriptors (Decs/Mesh), keywords, and their alternative terms were used for the search. To perform the search, Boolean operators were used, and the following terms were defined: *Population [* ((Apert OR Crouzon) AND (Disease OR Syndrom*))*], Concept [* ((cognit* OR neurobehavioral OR neurocognit* OR neuropsyc*) AND (evaluation OR evaluations OR assessment OR "test" OR tests OR status OR development OR disorder OR disorders OR impairment OR impairments OR impaired OR function OR functions)] *and Context* (in any context).

Table 1

Presents the health descriptors (Decs/Mesh), keywords with their alternative terms and the mnemonic Concept and Content Population (PCC) used in the search strategy.

Mnemonics	P (Population)	C (Concept)	C (Context)
Descriptors / Keywords	"Apert Crouzon Disease" or "Apert Syndrome" or "Crouzon Disease" or Syndrome, Apert" or "Apert-Crouzon Disease" or "Apert Crouzon Disease" or "Disease, Apert-Crouzon" or "Apert Syndrome" or "Syndrome, Apert" or "Acrocephalosyndactyly (Apert)" or "Acrocephalosyndactyly, Type I" or "Acrocephalosyndactylies, Type I" or "Type I Acrocephalosyndactylies" or "Type I Acrocephalosyndactyly" or "Acrocephalosyndactyly, Type 1" or "Acrocephalosyndactylies, Type 1" or Acrocefalossindactilia Tipo II" or "Acrocephalosyndactylia Type II" or "Acrocefalosindactilia Tipo II" or "Acrocefalossindactilia Tipo 2" or "Acrocephalosyndactylia Type 2" or "Acrocefalosindactilia Tipo 2	"Functions, Cognitive Avaliation" or " Function, Cognitive Avaliation" or "Cognitive Functions Avaliation" or "Cognitive Function Avaliation" or "Cognitions Avaliation" or "Evaluation of cognitive impairment" or "Cognitive Performance Avaliation" or ""Functions, Cognitive Evaluation" or " Function, Cognitive Evaluation" or "Cognitive Functions Evaluation" or "Cognitive Function Evaluation" or "Cognitions Evaluation" or "Cognitive Assessment Screening Instrument" or "Neurobehavioral Cognitive Status Examination" or "Neurocognitive Test" or "Neurocognitive Tests" or "Testes Neuropsicológicos" or "Neuropsychological Tests" or "Pruebas Neuropsicológicas" or "Exame Cognitivo" or "Teste Neuropsicológico" or "Neuropsychological Assessment" or "Developmental Neuropsychological Assessment" or "Developmental Neuropsychological Tests" or " Repeatable Battery	In any context
Desc/Mesh	((Apert OR Crouzon) AND (Disease OR Syndrom*))	((cognit* OR neurobehavioral OR neurocognit* OR neuropsyc*) AND (evaluation OR evaluations OR assessment OR "test" OR tests OR status OR development OR disorder OR disorders OR impairment OR impairments OR impaired OR function OR functions))	In any context

Source: Bauru, 2022.

Among the 184 articles found (*Embase=74 references, Scopus=56 references, National Library of Medicine- PUBMED/MEDLINE= 34 references and in the VHL Salud Network - PAHO, WHO, BIREME, LILACS = 20 references),* 90 were excluded with the support of Mendeley *software*, as they were duplicates. After careful reading of the titles and abstracts of the remaining 94 articles, 46 were selected for a reading of the full text, and among them, 21 were selected because they addressed the research question.

Thus, the final sample of this study consisted of 21 articles. The study selection process was performed by two independent evaluators and is shown in Figure 1.

For the purpose of analysis, the articles were numbered 01 to 21 and called "studies". The results were presented in the form of tables and discursive reports. To comply with methodological rigor, the PRISMA tool adapted for scope review (TRICCO, AC et al., 2018)[33-34] was applied.

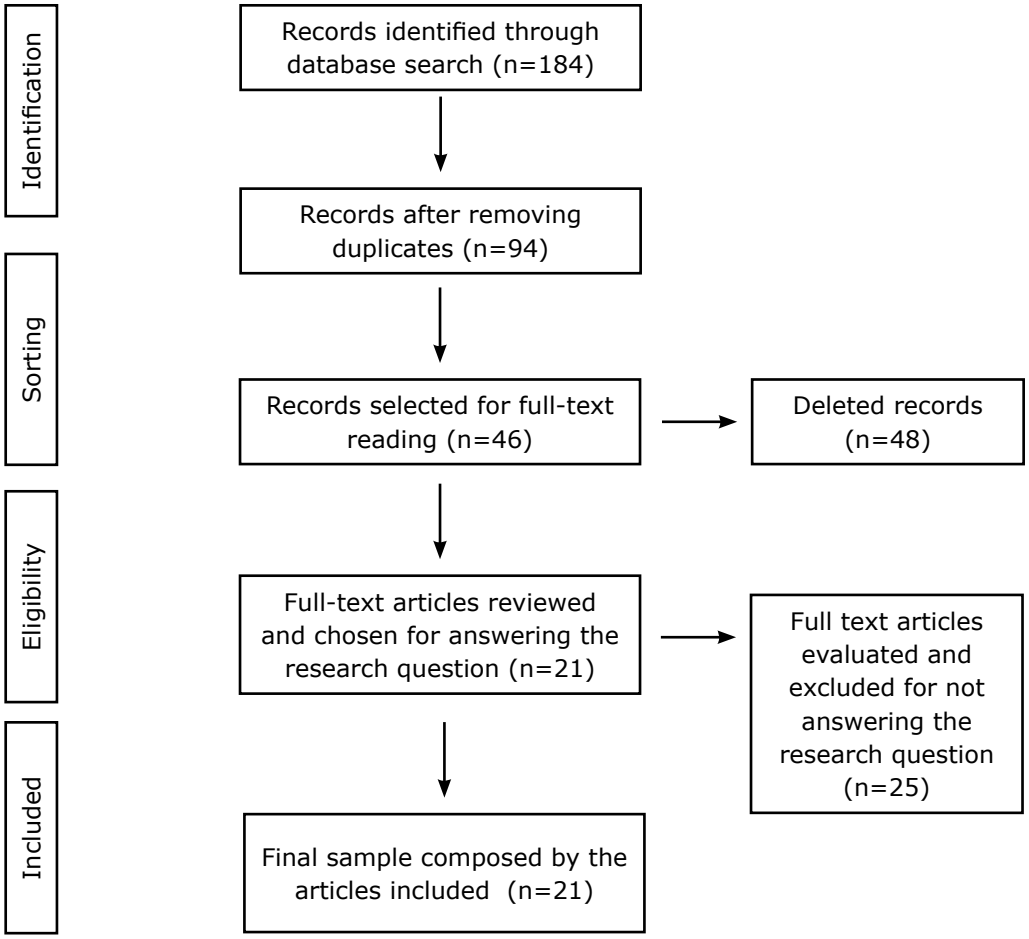

Figure 1: Flowchart of the studies selection process. Bauru, 2022.

RESULTS

Among the 21 studies, 19 publications were published in English (90.48%) in the past 40 years on the following continents: America, Europe, Africa, and Oceania. Brazil had the largest number of publications with six (28.5%), followed by the United Kingdom with four (19.0%), the USA with three (14.3%), Australia with two (9.5%), France with two (9.5%) and Spain, Greece, the Netherlands, and Nigeria with one (4.8%).

Table 2
Presents the studies according to authorship (principal author), year of publication, study title, country of publication, and place (institution) where the study was conducted.

Study	Authorship	Publication year	Title	Country of Publication	Location where the study was carried out
E1	Tara L. Wenger M. et al.	2019	Apert Syndrome Synonym: Acrocephalosyndactyly Type I	U.S.A.	Seattle Children's Hospital
E2	Hilton C. et al.	2019	Fingers Matter: The Development of Strategies for Solving Arithmetic Problems in Children With Apert Syndrome	United Kingdom	UCL Institute of Education, University College London
E3	Paternoster G. et al.	2019	SYM9.9C Cognitive Assessment in School Age Crouzon and Pfeifer after early Fronto-facial Monobloc	France	French National Reference Center for Craniofacial malformations, Hospital Necker Enfants Malades e Clinique Marcel Sembat
E4	Kana M. et al.	2018	A 37-year-old Nigerian woman with Apert syndrome - medical and psychosocial perspectives: a case report.	Nigeria	Kaduna State University
E5	Hilton C. et al.	2017	An Exploration of the Cognitive, Physical and Psychosocial Development of Children with Apert Syndrome	United Kingdom	UCL Institute of Education University College London
E6	Maximino L. et al.	2017	Syndromic craniosynostosis: neuropsycholinguistic abilities and imaging analysis of the central nervous system.	Brazil	USP-Bauru, Rehabilitation Hospital for Craniofacial Anomalies
E7	Fernandes M. et al.	2016	Apert and Crouzon syndromes-Cognitive development, brain abnormalities, and molecular aspects	Brazil	USP-Bauru, Rehabilitation Hospital for Craniofacial Anomalies
E8	Stavroussi P. et al.	2016	An examination of language and nonverbal abilities in twins with Apert syndrome	Greece	University of Thessaly
E9	Maliepaard M. et al.	2014	Intellectual, behavioral and emotional functioning in children with syndromic craniosynostosis.	Netherlands	Sophia Children's Hospital, Erasmus University e Vrije University
E10	Flapper W. et al.	2009	Intellectual Outcomes Following Protocol Management in Crouzon, Pfeiffer, and Muenke Syndromes	Australia	University of Adelaide

Study	Authorship	Publication year	Title	Country of Publication	Location where the study was carried out
E11	Yacubian-Fernandes A. et al.	2009	Cognitive development in Apert Syndrome and Crouzon Syndrome patients: a multidisciplinary model for evaluation	Brazil	USP-Bauru, Rehabilitation Hospital for Craniofacial Anomalies
E12	Yacubian-Fernandes A. et al.	2007	Crouzon syndrome: factors involved in neuropsychological development and quality of life	Brazil	USP-Bauru, Rehabilitation Hospital for Craniofacial Anomalies
E13	Da Costa A. et al.	2005	Neuropsychological diversity in Apert syndrome: a comparison of cognitive profiles.	Australia	Royal Children's Hospital, Victoria University
E14	Yacubian-Fernandes A. et al.	2005	Apert syndrome: factors involved in the cognitive development	Brazil	USP-Bauru, Rehabilitation Hospital for Craniofacial Anomalies
E15	Shipster C. et al.	2002	Speech and language skills and cognitive functioning in children with Apert syndrome: a pilot study	United Kingdom	Great Ormond Street Hospital NHS Trust, University College London
E16	Ciasca S. et al.	2001	Neuropsychological and phonological evaluation in the Apert's syndrome: study of two cases.	Brazil	Faculty of Medical Sciences, State University of Campinas, Unicamp
E17	Aguado A. M. et al.	1999	Neuropsychological implications of Crouzon syndrome: a case syndrome: a case report	Spain	Hospital Central de Astúrias, Universidade de Oviedo
E18	Renier D. et al.	1996	Prognosis for mental function in Apert's syndrome.	France	Hôpital Necker-Enfants Malades, University of Paris Descartes
E19	Campis L. et al.	1991	Children with Apert syndrome: developmental and psychologic considerations	U.S.A.	Children's Hospital, Harvard Medical School
E20	Patton M. et al.	1988	Intellectual development in Apert's syndrome: a long term follow up of 29 patients.	United Kingdom	Great Ormond Street Hospital NHS Trust, University College London
E21	Belfer M. et al.	1979	Body Image and the Process of Reconstructive Surgery	U.S.A.	The Children's Hospital, Harvard Medical School

Source: Bauru, 2022.

Table 3
Presents the studies according to the types of cognitive assessment methods used to assess the patient.

Evaluation method	Study
Wechsler Intelligence Scale with its multiple variations adapted to the age group of the examinee and its various subtests[25-32,36-39]	3, 6,7, 8,11, 12, 13, 14, 15, 16, 17, 18
(Wechsler Intelligence Scale for Children Test WISC-III) (Wechsler, 1994)[25-32,36-39]	6, 7, 9, 11, 12, 13, 14, 16, 18
Wechsler test for adults-WAIS[25-32,36-39]	6, 7, 11, 12, 14, 17
Nonverbal Wechsler Test[25-32,36-39]	3, 8
Wechsler Test for children -WISC IV[25-32,36-39]	3
Wechsler Test for preschool children -WPPS1[25-32,36-39]	11
Numerical Key Wechsler Test[25-32,36-39]	17
Wechsler-WAIS Test, Visual Perception subtest[25-32,36-39]	17
Wechsler-WAIS Test, Incomplete Figures subtest[25-32,36-39]	17
Wechsler-WAIS test, Vocabulary subtest[25-32,36-39]	17
Wechsler-WAIS Test, Arithmetic Problem Solving subtest[25-32,36-39]	17
Wechsler-WAIS Test, Comprehension subtest[25-32,36-39]	17
Wechsler-WAIS Test, Image subtest[25-32,36-39]	17
Wechsler-WAIS test, Cubes subtest[25-32,36-39]	17
Wechsler-WAIS Test, Reasoning Similarities subtest[25-32,36-39]	17
Wechsler-WAIS Test, subtests block design[25-32,36-39]	17
Intelligence Quotients (verbal intelligence, general intelligence, performance, and full-scale intelligence)[25-32,36-39]	6, 7, 11, 13, 18, 20
Token Test by: (De Renzi e Vignolo) and (Di Simoni) -XX[25-32,42]	6,11
Test of Everyday Attention for Children (TEA-Ch)[25-32,42]	3, 13
Stroop Test[25-32,42]	6, 11
Peabody's Picture Vocabulary Test[25-32],	6, 11
Raven's Progressive Matrices (PM-47) -XXX[25-32,40]	3, 8
British Ability Scales (BAS II)— First-year version (age group 2; 6–5; 11)[25-32,43-44]	9, 15
Questionnaire on Resources and Stress by Friedrich, Greenberg, and Crnic[61]	11, 12
Go-No Go Task[25-32,62]	17
Clinical Interview Method to Examine Children[25-32,56]	2
Gelman and Gallistel's Counting Principles Tests (1978)[25-32,57]	2
Assessment of counting skills and early arithmetic by the Hughes's boxes Test (1986)[20,25-32]	2
Evaluation and screening of number sense by the Jordan & Hanich's Test[25-32,53]	2
Assessment of numerical knowledge by the Griffin and Case's Test[25-32,59]	2
Assessment of finger gnosis by the method of Gracia-Bafalluy and Noë[25-32,54]	2
Braun and Clarke's approach to reflexive thematic analysis[25-32,63]	2
Subitizing and comparison Test[25-32]	2
Assessment of Counting Techniques by the Counting Test[25-32,53-54,57]	2
Assessment of Strategies to solve arithmetic problems[25-32,53-54,57]	2
Assessment of Different Ways of Using the Fingers[54]	2
Assessment of changes in finger gnosis[54]	2
London Tower Test[25-32,43]	3
Corsi block test[25-32,64]	3
Comprehensive Neuropsychological Battery for children ages 3–12 (NEPSY-II)[25-32,35]	3
Patient Health Questionnaire-9 (PHQ-9)[45]	4
Stanford-Binet Intelligence Test and Scale (L-M form)[25-32,41]	6
Λ-α-T-ω Test (a psychometric instrument for measuring linguistic competence)[25-32]	8
Child Behavior Checklist (CBCL/6-18)[65]	9

Evaluation method	Study
Disruptive Behavior Disorders Rating Scale (DBDRS)[66]	9
National Institute of Mental Health Diagnostic Interview Schedule (DIS)	9
Terman Merril Test (LM)[25-32,67]	11
Gesell and Amatruda Developmental Test[25-32,68]	11
Stein Test[25-32]	11
Vineland Adaptive Behavior Scales[25-32,69]	13
Assessment of Mastery of Daily Living Skills[30]	13
Assessment of Domains of Social Knowledge and Socialization[30]	13
Assessment of Mastery of Motor Skills[30]	13
Preschool Assessment (CELF-Preschool)[25-32]	15
Preschool Language Scale-3 (PLS-3)[70]	15
Great Ormond Street Speech Assessment (GOS. SP. ASS)[71]	15
Central Auditory Processing (CAP) Assessment (PAC)[72]	15
Vocal Pro ® Le Analysis	15
Assessment of the speech and language skills and cognitive functioning by the Brodsky, Crysdale and White's Scale[73]	15
Luria-Nebraska Neuropsychological Battery (LNNB)[4]	16
Phonological Awareness Test (PAT)[30]	16
Written Number-Symbol Pairing Test (Smith Test)[75]	17
Symbol Digit Modalities Test (SDMT)[25-32]	17
Written Number-Symbol Pairing Test (Smith Test)[75]	17
Rivermead Behavioral Memory Test (RBMT))[25-32]	17
Rey Complex Figure Test[25-32,76]	17
Krug Clinical Analysis Questionnaire (CAQ)[25-32]	17
Brunet-Lézine Scale of Development [77]	18
Goodenough–Harris Draw-a-Person Test[70-79]	21
Piers-Harris Test (applied to the patient and his mother) - Piers-Harris Self-Concept Scale[46]	21
Sears Test[25-32]	21
Conduct Inhibition Test (Drawn Test)[25-32]	17
Language Behavioral Observation Test (PROC)[25-32,47]	6
Boston Naming Test [25-32,80]	17
Palographic Test [25-32]	17

Source: Bauru, 2022.

DISCUSSION

When identifying the cognitive assessment methods applied to patients with Apert and Crouzon syndrome in the 21 studies, 75 types of cognitive assessment tests were used, most of which were internationally validated. There was no standardization of cognitive development assessments or defined protocol followed by the various units of care for patients with syndromic craniosynostosis, especially concerning Apert and Crouzon. This lack of standardization made it difficult to compare the neuropsychomotor and cognitive development profiles of these populations and allowed only a comparison of the general characteristics. The analysis of the cognitive evaluations applied to the patients of the analyzed studies showed the need for a more thorough neuropsychological evaluation that provides a more detailed developmental profile of patients with Apert and Crouzon syndromes, especially in those with Apert syndrome, due to the great phenotypic heterogeneity they presented.

The main cognitive assessment method applied in the 21 studies selected for this scope review was the **Wechsler Intelligence Scale** (with its multiple variations adapted to the age group of the examinee and its various subtests), which was applied to 12 of 21 studies (3, 6, 7, 8, 11, 12, 13, 14, 15, 16, 17, 18) analyzed (57.14%)[21,25-29,31,35-39].

Regarding the multiple variations of the Wechsler Intelligence Scale adapted to the age group of the examinee, it was observed that the tests were performed in the following descending order of application frequency:

- Wechsler test for children-WISC III (6 to 16 years), nine studies (42.86%)
- Wechsler test for adults-WAIS (16 to 90 years), six studies (28.57%)
- Nonverbal Wechsler test (4 to 21 years old), two studies (9.52%)
- Wechsler test for children-WISC IV (6 to 16 years), one study (4.76%)
- Wechsler test for preschool children (2 to 7 years old)-WPPS1, one study (4.76%), which is in agreement with the age group of the patients studied. Analyzing the age group of the population evaluated in the 21 studies of this scope review, it is observed that the age of the subjects ranged from 0 to 37 years with the following distribution:
- infants – 0 to 2 years old, assessed in six studies (28.57%),
- preschoolers – 3 to 7 years old, assessed in nine studies (22.86%),
- schoolchildren - 8 to 12 years old, assessed in 17 studies (80.95%),
- adolescents – 13 to 19 years, assessed in 13 studies (61.90%),
- adults – older than 20 years, assessed in eight studies (38.01%). Therefore, the population subjected to cognitive assessment was predominantly in two age groups: schoolchildren and adolescents, that is, from 8 years and 0 months to 19 years and 11 months.

Regarding the various subtests of the Wechsler Intelligence Scale [21,25-27,29,31,32,38-39], the following subtests were performed: Numerical Key, Visual Perception; Incomplete Figures; Vocabulary; arithmetic and solving arithmetic problems; Understanding; Image; Cubes; Similarities in Reasoning and Understanding of Comics; all were applied in only one study.

The Wechsler Intelligence Test nonverbally assesses the intellectual capacity of children and young people from 4 to 21 years of age and was developed to evaluate linguistically and culturally diverse individuals and individuals with limited verbal skills, such as specific language disorders, hearing impairment, intellectual disability, and autism spectrum disorder, among others. In the international context, it is considered the gold standard for cognitive assessment [21,38-39].

The Wechsler Nonverbal Ability Scale[21] is an individual assessment of cognitive ability for ages 4 to 21 years, adapted from previous versions of the Wechsler Test to minimize nonverbal instructions while maintaining the subtest format and composite scores. The pictorial guidelines are exclusive to this evaluation and are used to communicate the guidelines of the subtests. The objective in developing this nonverbal assessment was to fairly assess individuals from culturally and linguistically diverse groups[17] .

The second most commonly used cognitive assessment method was the **Intelligence Quotient (IQ) test** (with its variations of verbal intelligence, general intelligence, performance and full-scale intelligence)[25-26,28,] which was applied in six studies (28.57%) of the total of 21 studies analyzed. It consists of the expression of the level of intelligence of an individual at a given time about the standard common to their age group. Some test items are visual, while many are verbal and range from problems based on abstract reasoning to concentration on arithmetic, vocabulary and general knowledge. In the General Intelligence Factor (G), the IQ tests measure general intellectual development, namely, the Binet-Simon Scale, Stanford Binet Scale, WAIS - E*scala Wechsler para Adultos*, *WISC - Escala de Inteligência Wechsler para Crianças*, *Matrizes Progressivas de Raven* and *Escala de maturidade mental Colúmbia*. In 1916, Lewis Terman proposed the following classification:

- 130 and above: Very Superior
- 121-130: Superior
- 111-120: High Average
- 90-110: Average
- 80-89: Low Average
- 70-79: Borderline
- Scores Under 70: Extremely Low rage[25-30,36-38,41]

In analyzing the frequency of application of the cognitive evaluation of patients with Apert and Crouzon in the 21 studies, the third most popular tests, which were used in two studies each (9.52%), were Token [42], Attentional Functions (TEA-Ch[26.29], Stroop[42], Peabody's Figure Vocabulary, Raven's Progressive Matrices[23], and British Ability Scale 2 (BAS-II)[43-44].

In six of the 21 studies selected (3, 11, 12, 14, 15, and 21), the caregivers completed the tests,

questionnaires, and interviews given the disabling cognitive impairment of the assessed patients:

1) Friedrich, Greenberg, and Crnic Simplified Resource and Stress Questionnaire (QRES)[45], which measures the stress of parents of children with developmental disorders, was used in three studies (11, 12, and 14), corresponding to 14.29% of the total of 21 analyzed studies.

2) The Piers-Harris test (applied to the patient and his or her mother)[46] evaluates the self-concept of children and adolescents 7 to 18 years old. It monitors changes in self-concept over time and identifies individuals who will need future evaluative or therapeutic interventions. It is a 60-item self-report questionnaire with the subtitle "How I feel about myself". It comprises six domains: a) Behavioral Adjustment, b) Freedom from Anxiety, c) Happiness and Satisfaction, d) Intellectual and School Status, e) Physical Appearance and Attributes, and f) Social Acceptance. It uses two validity scales that identify biased responses and the tendency to respond randomly. It was used in Study 21, that is, in 4.76% of the 21 studies analyzed.

3) The Sears Test[47] consists of evaluation forms for children (8 to 12 years old) and for adolescents (13 to 18 years old), teacher and parent report forms. The forms can be used in any combination of student, parent, and teacher assessment and measure constructs of self-regulation, responsibility, social competence, and empathy, in addition to items designed to capture the unique perspective of the rater. The items are expressed as positive desirable characteristics. The forms reflect the overall construction of social resilience and are practical for repeated evaluation (monitoring of progress). The test was used in Study 21, corresponding to 4.76% of the total of 21 studies analyzed.

4) Semistructured interviews asking parents about the type of school their child attends, the interventions performed, and current concerns about their child's development were employed in Study 15, corresponding to 4.76% of the total of 21 studies analyzed.

5) A brief questionnaire (unspecified) was used in Study 3 (4.76%).

In addition to the cognitive assessment tests applied to the patients and their caregivers, multidisciplinary assessment tests were added, the latter complementing the results of the former and thus obtaining greater detail about the performance of patients with Down syndrome. As a result, the profile of these patients was more precisely defined in terms of their strengths and difficulties and concerning their learning. The following multidisciplinary assessment tests were performed:

a) Speech-language pathology evaluation**:** pure tone audiometry and tympanometry

b) Radiological evaluation: Brain magnetic resonance imaging (MRI) and SPECT

c) Genetic evaluation: Exome

d) Orthodontic and dental evaluation

e) Socioeconomic evaluation**:** the Graciano, Lehfeld and Neves Methodology [59], which consists of parameters used in socioeconomic analysis and portrays situations encountered socially, was used as a tool for understanding the usufructuary's reality and allowing intervention. Its indicators are socioeconomic status, number of family members, education, occupation, and housing. These items were systematized in a "Socioeconomic assessment tool". It was used in three studies (11, 12, and 14), corresponding to 14.29% of the 21 studies.

When analyzing the population profile of the 21 studies that make up this scope review, the following characteristics stand out:

A) Syndromic diagnosis

Three distinct groups were identified: a) the studies evaluated patients with Apert syndrome. This was the largest group, comprising 13 studies (1, 2, 3, 4, 5, 8, 13, 14, 15, 16, 18, 19, 20) and accounting for 61.90% of the 21 analyzed studies; b) the studies evaluated patients with Crouzon syndrome, and this group included four studies (7, 10, 12 and 17), that is, 19.05% of the 21 studies; c) four studies evaluated a mixed population of patients with both Apert and Crouzon syndromes (Studies 6, 9, 11, 21), representing 19.05% of the 21 studies. Therefore, in this scope review, a larger number of studies analyzed patients with Apert syndrome. This is probably because there are a larger number of studies in the literature because Apert syndrome is more complex (greater number of associated malformations in the same individual), more varied (several phenotypes), with a higher frequency of cognitive impairment and greater severity of neuropsychomotor development delay when compared to Crouzon syndrome[6,8,10,22-23]. Therefore, more interventions from health teams, schools and caregivers and greater knowledge about the pathology are needed.

B) Origin (institution, city, country)

Among the 21 studies in this scope review, regarding the bibliometric indicators, Brazil was the country with the largest number of published studies, with six studies, that is, 28.5% of the total, five of which were conducted at the Hospital for Rehabilitation for Craniofacial Anomalies of the University of São Paulo (USP) in Bauru and one at the Hospital of the School of Medical Sciences, University of Campinas, Unicamp. Therefore, the Hospital for Rehabilitation of Craniofacial Anomalies of USP Bauru stands out as the center for assistance to patients with craniofacial malformations and was the largest scientific producer in this review [8-10,14,17,23].

C) The date of publication of the studies

The analyzed articles comprised the period from 1997 to 2019, with the majority published in 2019, indicating that this is a current research topic.

Regardless of the type of cognitive assessment test used, individuals with Apert have a wide range of phenotypes ranging from normal intellect or mild intellectual disability to moderate to severe intellectual disability[10,14]. Patients with Crouzon syndrome have satisfactory cognitive skills, based on the reports of their parents, self-evaluations and results of the numerous cognitive evaluation tests. Crouzon syndrome is not associated with a poor cognitive prognosis [3-4,9-10,14-16,22-23], which is perhaps why in the literature, there are few specific studies for Crouzon when compared to Apert.

Regarding children with syndromic craniosynostosis, analyzed studies reported that they have IQs similar to the general population, but these children are potentially more at risk of developing intellectual disabilities and social problems; for this reason, early and comprehensive rehabilitation is crucial and should be offered in a multidisciplinary manner and at the optimal time so that these children become independent adults with satisfactory quality of life. To this end, rehabilitation programs should be designed to focus on the affected cognitive functions[1,4,6,9,14-15,49].

To offer individualized rehabilitation programs focused on the affected cognitive functions, most of the selected studies point to the same path: due to the heterogeneity of cognitive changes (presented by the various syndromic craniosynostoses and even the various phenotypes within a syndrome), there is a need for a careful and multidisciplinary neuropsychological evaluation[2,10,16,49-50]. The studies agree that the environment in which children with Apert and Crouzon develop affects their development and future potential, and an environment with scarce resources and deprived families results in lower IQs among this population[5,9,22,49].

The studies agree that more research is needed to deepen the knowledge regarding the predictive and correlative risk factors in Apert and Crouzon syndromes, making it possible to better address the functional capacities and needs of these children and allow for more effective educational inclusion.

Analyzing the cognitive evaluations applied to patients with the Apert and Crouzon syndromes report the same results about the performance of language, attention, memory, reasoning, strengths and difficulties concerning learning and development[2,4-10,12-19,22-24,49-51]. Exploratory analyses tested differences between subgroups of children with the various types of syndromic craniosynostosis, and among these, the children who obtained the lowest levels of Global Functional Intellectual Quotients were those with Apert. Children with Apert and Crouzon had the highest ratings of socialization, attention and internalization disorders compared to children in the normative group who did not have intellectual deficits. Children with Apert had the worst neuropsychological and cognitive outcomes [6,16,50].

The results of the various studies analyzed were also in agreement regarding the factors that affect the neuropsychomotor development of patients with Apert and Crouzon, namely, intracranial pressure, brain malformations, genetic factors, age at surgical correction, psychosocial factors, institutionalization, quality of the family environment, caregivers' education and socioeconomic level [2,5-10,12-19,22-24,49-52].

Regarding the age at surgical correction, the cognitive development results for children born with Apert and Crouzon syndromes are currently more promising than those previously reported in the literature because surgical and multidisciplinary management has become more advanced and children have had access to intervention programs earlier. Postponement of the first surgery after 1 year of age was associated with a lower IQ. Cognitive analysis of the patient is important because it defines the profile of disabilities and guides the health team regarding the most appropriate time for corrective surgery and postoperative follow-up[10-12,15-16,24].

Study 2 (E2) provided strong evidence that the exploration of finger gnosis should be encouraged in children with Apert to prevent them from having low performance in their initial arithmetic skills. Given that finger gnosis develops very rapidly in the first six years of life in typically developing children, the present study proposed that children with Apert should be encouraged to develop finger use and undergo corrective hand surgery as early as possible; otherwise, hand abnormalities put them at risk of delay in the development of their initial arithmetic skills. Since the fingers influence the development of arithmetic skills, orthopedic surgical interventions in the hands of patients with Apert have a significant impact on the cognitive development of these children[18,53-54].

Another factor that should be considered in the evaluation of the global and cognitive development of patients with Apert and Crouzon is the molecular aspect. The literature reports that patients with Apert with the p. SerS252Trp mutation have more severe ocular phenotypes. The p. Pro253Arg mutation is associated with more severe disease in relation to syndactyly and cognitive outcomes. In this review, Study E7 presented a patient with Apert and p. Pro253Arg mutation who had an FSIQ of 108 and a higher IQ than patients with Apert and p. SerS252Trp mutations[1,3-4,9-10,15,50-51]. In the literature, several studies have attempted to correlate the IQ of patients who had Apert with central nervous system abnormalities (hypoplasia of the septum pellucidum, malformation of limbic structures, abnormalities in the corpus callosum, megalencephaly, gyrus abnormalities, encephalocele, pyramidal tract abnormalities, white matter, gray matter heterotopia, and Chiari I deformity)[5,8-10,15-16,19,23,50]. The L1 cell adhesion molecule (L1CAM) gene plays an important role in white matter development, and to exert its function, it must interact with FGFRs. As FGFR defects lead to craniosynostosis syndromes, FGFR defects can generate brain abnormalities due to a lack of interaction with L1CAM, producing primary white matter defects. More studies are needed to establish a better correlation between the genetic alterations, the phenotype, and the intensity of the cognitive deficit in Apert and Crouzon syndromes[10].

The studies analyzed unanimously agreed that environmental factors (social aspects, quality of life, parental education level and occurrence of institutionalization) influence cognitive development because in environments with limited resources, patients with Apert and Crouzon become adults with less education, marry less, have fewer friends, have lower employability (resorting to begging for a living, as described in article E4) and have a greater dependence on third-party care in adulthood[2,5-10,12-19,22-24,49-51]. In this review, Study E16 stood out because it was the only study that reinforced the need to perform neuroimaging to establish the presence or absence of hypoperfusion in the temporal area in cases of the phonological disorder. More studies correlating the results of cognitive assessment and the pattern in functional neuroimaging are needed[17].

The limitations of this scope review are due to bibliometric factors, such as 1) the small number of studies related to the topic of this review and 2) the small number of patients studied in the 22 years of scientific production analyzed in this scope review; the largest sample of patients with Apert was 60, and the largest sample of patients with Crouzon was 113[13,16].

CONCLUSION

This scope review showed that the topic "Cognitive assessment methods of patients with Apert and Crouzon syndrome" has been better explored in recent years, mainly due to the expansion of cognitive assessment methods and the evolution of surgical techniques for correction of craniofacial malformations that are applied in patients with syndromic craniosynostosis, especially in Apert and Crouzon syndromes. It is noteworthy that despite the wide variety of cognitive tests available for the evaluation of these patients [20,53-57,59,60], there is no well-defined protocol that is a standard to be followed by the various centers of care for patients with syndromic craniosynostosis. This lack of a well-defined protocol standardization for the investigation of the cognitive profile of patients with Apert and Crouzon syndromes, together with the great variability of phenotypic presentation, especially in Apert syndrome, make it very difficult to compare the results of the various studies performed at Centers for Craniofacial Malformations around the world. It is also important to note that in settings with limited resources, such as in developing countries, medical and psychosocial interventions organized to care for these patients and support their families are scarce,

which could result in a future with poor quality of life and a greater level of disability And IQ in patients with Apert and Crouzon syndromes.

Regarding the literature review, this scope review showed some gaps to be filled:

- The need for a more thorough neuropsychological evaluation of patients with Apert and Crouzon syndromes, especially patients with Apert syndrome, considering the great heterogeneity of phenotypes (and cognitive changes determined by these phenotypes) in the latter.

- The urgent need to create public health policies that promote specific and planned rehabilitation programs focused on the affected cognitive functions of patients with Apert and Crouzon in developing countries.

- More studies are needed to monitor and better understand the cognitive abilities of patients with Apert and Crouzon, as well as specific studies to validate new cognitive assessment tools.

- More research is needed to deepen the knowledge regarding the predictive and correlative risk factors in Apert and Crouzon syndrome, making it possible to better address the functional abilities and needs of these children.

- More studies are needed to standardize the cognitive evaluation of patients with Apert and Crouzon syndromes.

Implications for research

This scope review showed that despite the existence of numerous validated cognitive assessment methods available in the literature for application in patients with Apert and Crouzon syndromes, there is still a need for more studies to be conducted with the objective of creating instruments and methods (such as scales, exams and tests) that investigate in detail the cognitive abilities and disorders of patients with the Apert and Crouzon syndromes. It also showed that although there are numerous validated cognitive assessment methods available in the literature for application in patients with Apert and Crouzon with the intention of assessing their functional capacities, there is still a need for studies to define a cognitive evaluation protocol that standardizes the investigation of cognitive performance (language, attention, memory, reasoning, behavior, strengths and difficulties about learning, ability to socialize and quality of life) of individuals with Apert and Crouzon. Standardization would facilitate communication and promote a greater exchange of information between the various care and research centers focused on patients with Apert and Crouzon syndromes.

Implications for practice

This review showed that studies conducted to cognitively evaluate patients with syndromic craniosynostosis, especially those with Apert and Crouzon syndromes, with the objective of profiling these patients, provided detailed information on the neuropsychomotor skills and difficulties, cognitive and psychosocial aspects of these patients to the health, school and caregiver teams, making the teams better able to meet the special needs of patients. Studies that provide greater knowledge about the difficulties and facilities in the acquisition of skills and the functional capacity of patients with Apert and Crouzon will make it possible to better meet the special needs of these patients and offer stimulation at the optimal time, which will promote the full cognitive development of these children and adolescents and enable them to become adults functionally capable of living independently with a satisfactory quality of life.

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