Patient-Reported Quality of Life in Highest-Functioning Apert and Crouzon Syndromes: A Comparative Study

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Background: Crouzon and Apert syndromes are the most common syndromic forms of craniofacial dysostosis. Apert syndrome has a broad clinical spectrum, including complex craniofacial involvement, as well as limiting deformities of the hands, feet, and other joints that require multiple surgical procedures when compared with Crouzon syndrome, which is generally less severe. The authors hypothesized that the quality of life of Apert syndrome patients is inferior to that of Crouzon syndrome patients.
Methods: The quality of life of Apert ($n = 8$) and Crouzon ($n = 12$) syndrome patients was assessed using the World Health Organization Quality of Life-100 questionnaire. The Mann-Whitney test was used to compare the quality-of-life scores between Apert and Crouzon patients. Values were considered significant for a confidence interval of 95 percent ($p < 0.05$).
Results: Apert patients showed an overall higher (score > 60 percent) quality of life in most World Health Organization Quality of Life-100 facets (68 percent) and domains (83.33 percent), with significance ($p < 0.05$) in three facets (energy and fatigue, mobility, and environment in the home), compared with Crouzon patients.
Conclusion: Contrary to the authors' initial hypothesis, both the highest-functioning Apert patients and the Crouzon patients presented a satisfactory quality of life, demonstrating that these syndromic patients had acquired the necessary repertoire to manage the adverse daily situations of their lives. (*Plast. Reconstr. Surg.* 133: 182e, 2014.)

Craniosynostosis is the premature fusion of one or more cranial sutures that affects one in every 2000 to 2500 live births and can occur in association with different syndromes.[1] Craniofacial dysostosis is the term applied to familial forms of craniosynostosis, in which the sutural involvement generally includes the cranial vault, cranial base, and midfacial skeletal structures.[2] Crouzon (one in 65,000 births) and Apert (one in 100,000 births) syndromes are the most common craniofacial dysostosis syndromes[2,3] and are caused by heterozygous mutations of the fibroblast growth factor receptor 2 gene (*FGFR2*) on chromosome 10.[1] Crouzon syndrome patients principally have craniofacial abnormalities, such as bilateral coronal craniosynostosis, exorbitism with hypertelorism, and maxillary hypoplasia with relative mandibular prognathism.[2–4] Apert syndrome patients present involvement of the craniofacial skeleton (bilateral coronal craniosynostosis and impaired development of the midface, with hypertelorism, exorbitism, and maxillary retrusion) and also exhibit debilitating extracraniofacial features, such as complex

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Received for publication April 2, 2013; accepted August 29, 2013.
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DOI: 10.1097/01.prs.0000437260.31693.75

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

Supplemental digital content is available for this article. A direct URL citation appears in the text; simply type the URL address into any Web browser to access this content. A clickable link to the material is provided in the HTML text of this article on the *Journal*'s Web site (www.PRSJournal.com).

symmetric acrocephalosyndactyly.[2–4] Interestingly, in addition to these severe dysmorphologic characteristics, Apert syndrome patients have been historically reported with variable degrees of neurodevelopmental delay, cognitive deficit, and mental retardation, while most Crouzon patients have nearly normal mental development and normal intelligence.[3–14]

In this context, Dr. Paul Tessier[15] defined three main reasons (functional, morphologic, and psychological) for the treatment of these syndromes. Hence, management of Apert and Crouzon syndromes has been best accomplished by an experienced multidisciplinary craniofacial team.[16,17] As Apert syndrome presents an extensive phenotypic variability, the surgical treatment of these patients requires an early intervention with multiple, complex reconstructive procedures (reaching up to 59 procedures in a single patient)[18–20] to decrease morbidity, improve neurocognitive function,[18] secure brain growth and visual acuity,[21] and also allow fingers independence and mainly the possibility of acquiring motor abilities at a very early age, approximating those in normal children.[20]

Although the effects of surgical interventions have been routinely assessed by objective measurement instruments such as cephalograms, computed tomography, and serial photographs,[18–20] clinical outcomes reporting on the treatment of craniosynostosis has been described as inconsistent and lacking in methodological rigor.[22] Thus, the application of alternative instruments to measure the effects of treatments becomes necessary.[22] Recent studies[23–25] indicate that among the existing parameters to measure the postoperative outcomes of craniofacial surgeries, a patient-reported quality-of-life instrument should be used because patient satisfaction with appearance, speech, and quality of life is ultimately the factor that may predict the ability of these patients with craniofacial abnormalities to integrate meaningfully into society and prevent the development of adjustment problems. Thus, the adoption of a well-validated, patient-reported quality-of-life instrument may predict patients at risk for future social problems and perhaps allow early intervention, which may help to enhance integration into society.[24,26] However, the literature specifically addressing patient-reported quality of life in Apert and Crouzon syndromes is relatively scarce,[20,27–29] although different aspects, such as clinical features, orbital volume, and midface cephalometric changes, among others, have been targets of comparative studies[4,30,31] between these syndromes.

Since Apert syndrome has a broad clinical spectrum, including complex craniofacial involvement, as well as limiting deformities of the hands, feet, and other joints,[2,3] which require multiple surgical procedures[18–20] when compared with Crouzon syndrome (which is generally less severe),[2–4] the authors hypothesized that the patient-reported quality of life of Apert syndrome patients would be inferior to that of patients with Crouzon syndrome. Therefore, the purpose of this study was to assess the quality of life of patients with Apert and Crouzon syndromes who were surgically treated at a single craniofacial institution.

PATIENTS AND METHODS

A retrospective observational study was conducted of patients clinically and genetically diagnosed with Apert or Crouzon syndromes who underwent surgical procedures at a single craniofacial institution. Those who presented with an uncertain diagnosis or who had cognitive deficits that did not allow them to answer questionnaires were excluded.

All patients were assessed with the previously validated Portuguese version of the World Health Organization Quality of Life-100 questionnaire.[32,33] For the interview, both the patient and a physician interviewer were gathered in a silent room. Completion of the World Health Organization Quality of Life-100 was performed exclusively by the participant. The questions were read to the patient with neither explanations nor interpretations given. Responses were scored using a 5-point Likert intensity scale, with the lowest rating being 1 and the highest rating being 5. Patients had the option of not answering the question. The developmental ability of the highest-functioning Apert patients to completely fill out the questionnaire showed that they were eligible to evaluate their quality of life based on their own judgment and perception.

All answers based on the World Health Organization Quality of Life-100 questionnaire were expressed in 24 facets and six domains (physical ability, psychological, independence level, environment, spirituality, and social relations). Scores for each domain ranged from 0 to 100.[32,33] The domain scores were divided into good (score > 60) or poor (score ≤ 60) quality of life according to a previously validated quality-of-life score cut-off.[34] Quality-of-life scores were not compared with any normative data, as there are no population norms available for the World Health Organization Quality of Life-100 questionnaire in Brazil.

The present study was approved by the Institutional Review Board and complied with the 1975 Declaration of Helsinki, as amended in 1983. All patients or their parents gave written informed consent.

Statistical Analysis

For the descriptive analysis, the mean was used for metric variables, and percentages were given for categorical variables. The measurements related to the quality-of-life analysis were summarized. The software program Statistical Package for Social Science (SPSS version 16.0 for Windows; SPSS Inc., Chicago, Ill.) was used to calculate the six domain scores. The Mann-Whitney test was used to compare the quality-of-life scores between Apert and Crouzon patients. Values were considered significant for a confidence interval of 95 percent ($p < 0.05$).

RESULTS

The present study consisted of 20 patients (90.91 percent) diagnosed with Apert ($n = 8$) or Crouzon ($n = 12$) syndrome. Twelve patients (60 percent; five Apert patients and seven Crouzon patients) were female and eight (40 percent; three Apert patients and five Crouzon patients) were male. Ages at application of the World Health Organization Quality of Life-100 questionnaire ranged from 6 to 36 years old, with an average age of 17.35 ± 7.67 years (15.5 ± 8.07 years for Apert patients and 18.58 ± 7.66 years for Crouzon patients). Two Apert patients (9.09 percent) were excluded due to a significant neurocognitive handicap and full inability to respond to all of the queries of the questionnaire. All of these patients are still being followed at our craniofacial institution (Figs. 1 and 2).

Quality-of-Life Analysis

Apert and Crouzon syndrome patients had scores greater than 60 in 22 facets (88 percent), with no scores lower than 50. Both Apert and Crouzon groups presented a high score (>60 percent) in all six World Health Organization Quality of Life-100 domains. Apert syndrome patients showed higher scores in 17 facets (68 percent) and in five domains (83.33 percent) than did Crouzon syndrome patients. Crouzon syndrome patients presented higher scores in eight facets (32 percent) (quality of life from the point of view of the interviewee, spirituality, opportunity in recreation and leisure, health and social care, physical safety and security, sexual activities, social support, and dependence on medications or treatments) and in one domain (16.67 percent) (spirituality) than Apert syndrome patients. The comparative analysis revealed that Apert patients had significantly ($p < 0.05$) higher scores in three facets (energy and fatigue, mobility, and environment in the home) than did Crouzon patients (Figs. 3 through 5 and Table 1).

DISCUSSION

The World Health Organization Quality of Life group[35] defined quality of life as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns." In this context, Habal[36] states that complex craniofacial procedures are mostly performed to improve quality of life and to prepare patients for a better future. Thus, as surgeons become aware that objective measurements of the craniofacial skeleton as indicators of satisfactory outcome in craniofacial surgery might not corroborate with the patient's satisfaction with the result and how it influences individual perceptions of his or her position in life, patient-reported quality-of-life outcome through quality-of-life instruments has gained popularity over the last 5 years.[23–26] When associated with clinical data, it has proven to be a useful tool for redirection of the multidisciplinary approach in order to optimize patients' rehabilitation.[23–26] The patient's adherence to a long treatment that may take more than two decades is indeed correlated with the patient's perception about himself or herself and the treatments.[18–20] Like others,[37] we sometimes identify patients in our craniofacial clinic with good aesthetic and cephalometric results who seem unhappy or reluctant to accept their residual deformity. Thus, the modern instruments of quality of life with a broad domain, which can assess physical appearance, psychological functioning based on the patient's social relationship with peers and with the environment, in addition to personal spiritual beliefs, are becoming preferred for obtaining such important data.[20,23,24,26] However, available instruments must undergo translation and cross-cultural adaptation.[38,39] These steps are important for the reliability and validity of the chosen instrument.[38,39] Instruments that are manually translated to another language may lead to outcomes reporting different results depending on the meaning and, subsequently, to an error in interpretation.[38,39] Because the World Health Organization Quality of Life-100

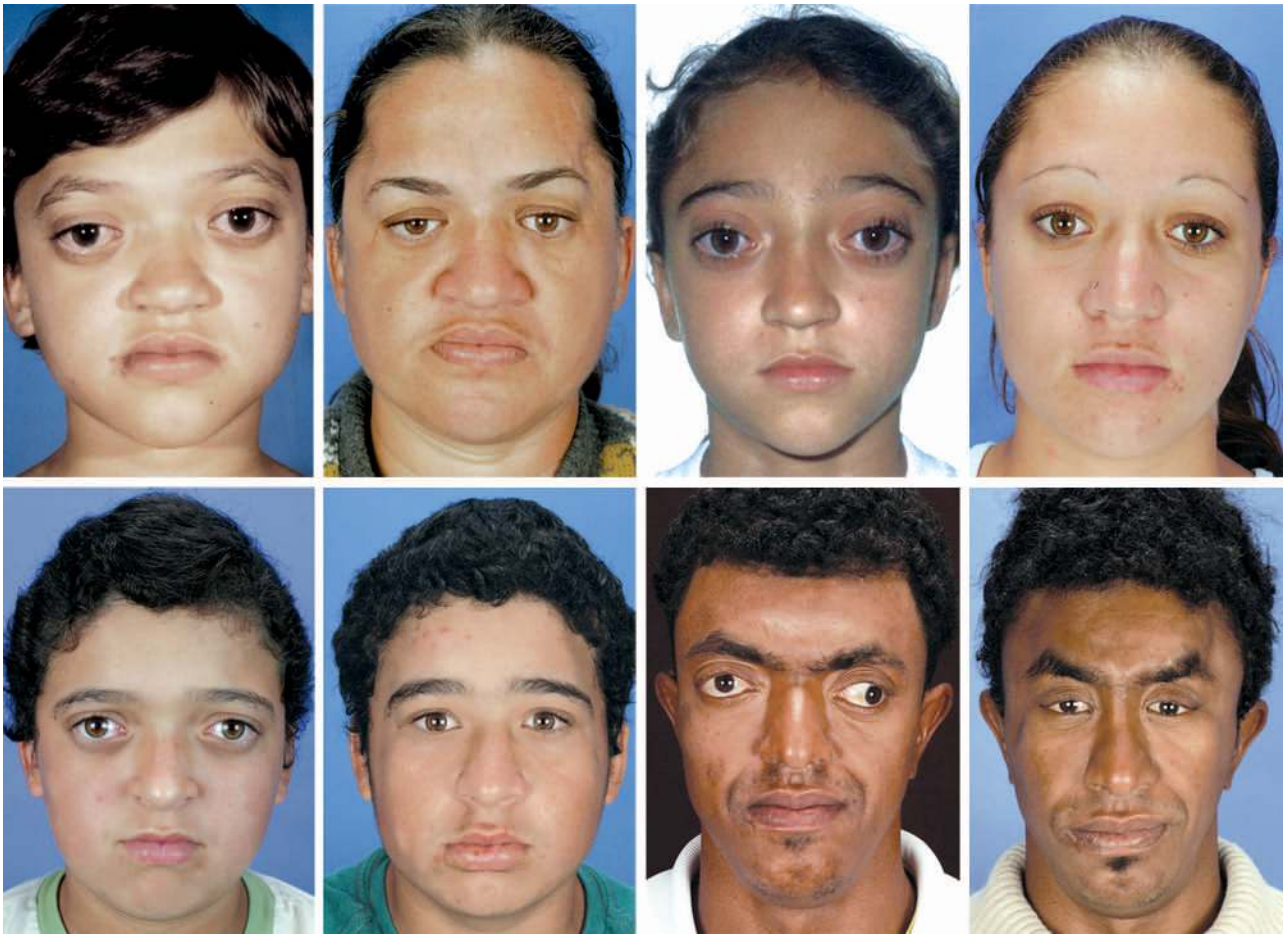

Fig. 1. (*Above* and *below, left* and *second from left*) Family with Crouzon syndrome who responded to the World Health Organization Quality of Life-100 questionnaire and who represent the evolution of craniofacial surgery in Brazil with modern distracter devices that allow bone stability to the midface advancement. (*Above, left*) The mother and progenitor underwent acute monobloc frontofacial advancement in 1985; (*above, second from left*) the mother is shown 28 years after the operation. (*Above, second from right*) The older daughter underwent monobloc frontofacial advancement with distraction osteogenesis in 1994; (*above, right*) she is shown 19 years after the operation. (*Below, left*) The youngest son underwent monobloc frontofacial advancement with facial bipartition associated with distraction osteogenesis using internal Kawamoto distracters (the Roman arch technique); (*below, second from left*) he is shown 5 years after the operation (craniofacial intervention performed in conjunction with Drs. James P. Bradley and Reza Jarrahy while they were visiting our institution in Brazil). (*Below, second from right* and *right*) Preoperative and postoperative views of a Crouzon patient who underwent monobloc frontofacial advancement with facial bipartition associated with distraction osteogenesis.

questionnaire had previously been translated and adapted to the Brazilian-Portuguese language and to the vast, multifaceted aspects of Brazilian culture,[32,33] it has been used extensively to measure patient-reported outcome in Brazil[40–42] in the absence of normative scores from the heterogeneous Brazilian population.

Syndromic craniosynostosis leads to a striking craniofacial dysmorphism in addition to the functional issues.[20,27–29,43] These combined factors can have a distinct influence on a patient's quality of life.[20,27–29,43] Clinical and radiological symptoms and signs of intracranial pressure, breathing issues, visual and hearing limitations, as well as delayed motor and language acquisition may directly affect the patient's capacity to report his or her quality of life.[20,27–29,43] Comparisons of syndromic craniosynostotic children with a normative population have shown that they present a significantly lower overall quality of life.[27,43] Among the group of craniosynostotic children, the authors[43] showed that Apert syndrome had the largest impact on different domains of a quality-of-life questionnaire. Since Apert syndrome may present a broad phenotypic variability with a significant range of neurodevelopmental status, assessment of the severity

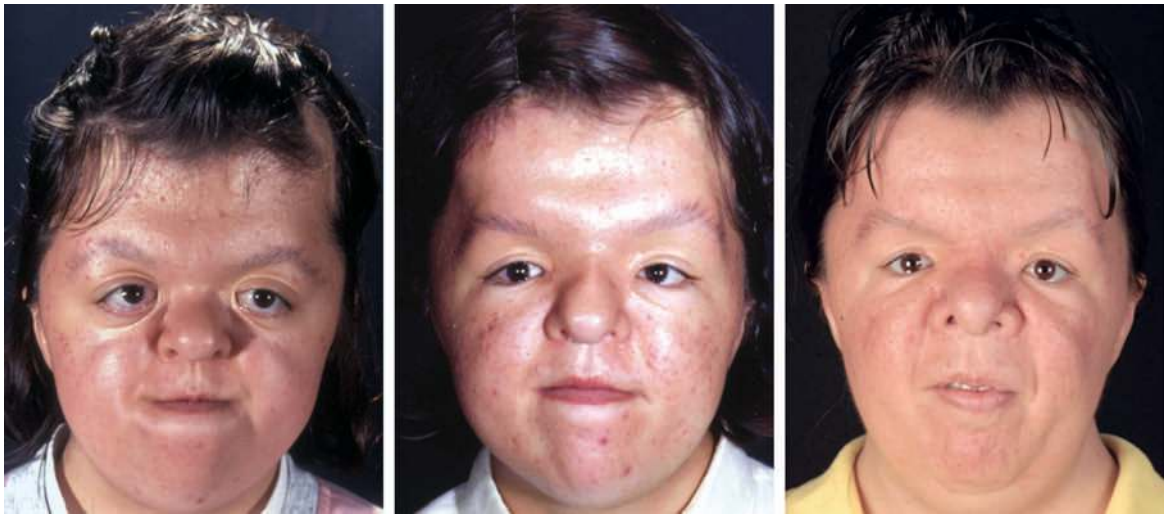

Fig. 2. (*Left*) Preoperative view of a 10-year-old Apert patient who underwent monobloc frontofacial advancement. (*Center)* Postoperative view of the same patient at 1 year after surgery. (*Right*) Postoperative view of the same patient at 17 years after surgery. The Le Fort I advancement was performed 7 years after the monobloc advancement.

of the intelligence quotient varies among studies[5,8,11,14] from 32 percent to 77.8 percent. While authors[8] have associated low neurodevelopmental status with low social and educational degrees, others[19] have associated the higher number of operations with lower neurodevelopmental levels. According to Da Costa et al.,[5] although syndromic craniosynostic children present a significantly lower intelligence quotient in comparison to the normal population, they show similar skills fitting into normative data. However, the motor abilities of Apert syndrome are highly correlated with the adherence to a strict treatment protocol.[20]

Fearon and Podner[19] stratified the neurodevelopmental status of Apert syndrome into three levels: level A, normal to mild delay; level B, moderate delay; and level C, profound delay. The finalization of a quality-of-life questionnaire among patients with Apert syndrome demands a level A status. Thus, we included only Apert patients who had adhered to our protocol and had shown the capacity to respond to all of the questions on the questionnaire. These inclusion criteria, inherent to the methodology of health-related quality-of-life instruments, created a selection bias by selecting the highest-functioning Apert patients and excluding those with moderate and profound delay. On the other hand, since others[5–7] have also shown that patients with Crouzon syndrome present a normal intelligence quotient, all recruited Crouzon patients of our cohort could appropriately respond to the quality-of-life questionnaire.

Our data show that both Apert and Crouzon syndrome patients presented an overall high score (>60 percent) in all domains of the quality-of-life instrument, despite the exhaustive average number of surgical procedures, hospitalization days, and familial distress experienced by the patient and his or her family owing to the complexity of the treatment and eventual surgical complications. Interestingly, others[44] have also shown that this population functions quite well. Tovetjärn et al.[45] demonstrated that although adult Apert syndrome patients had statistically less experience with sexual relationships, lower level of education, fewer friends, lower marital status, lower level of social network, more frequent difficulties with sports, and more depressive mood periods than healthy controls, there was no difference between these groups regarding a generally positive attitude toward life. According to the authors,[45] the explanation for the relatively low social situation can be associated with the poor aesthetic outcomes early in life that compromise the development of progressive social interaction with peers. These findings corroborate with those of others[46] who identified a satisfactory social relationship in syndromic patients who had undergone major craniofacial procedures such as monobloc advancements or subcranial Le Fort III. We believe that the major craniofacial operation is one fundamental factor that justified the overall high quality of life in these patients. However, the role of the multidisciplinary team facilitates the patient and family environment by means of routine psychological support and social worker help, counseling and collaboration with school teachers, and decisions regarding the patient's social engagement and adherence to postoperative follow-up.

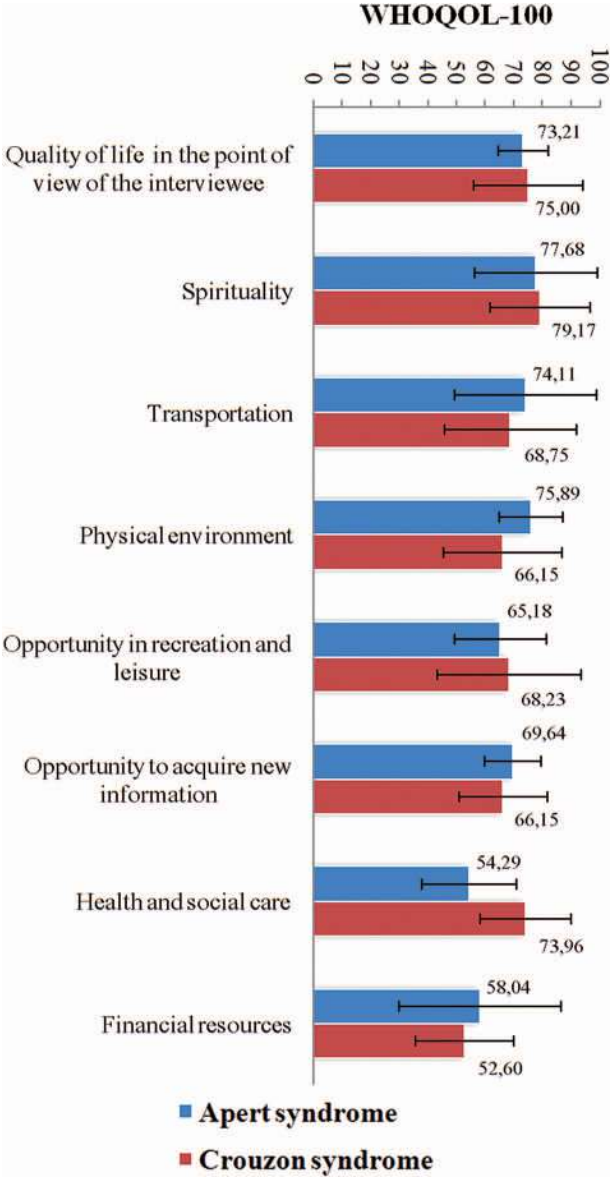

Fig. 3. Quality of life of Apert or Crouzon syndrome patients based on World Health Organization Quality of Life-100 (*WHOQOL-100*) facets. There were no significant differences ($p > 0.05$) between the two groups.

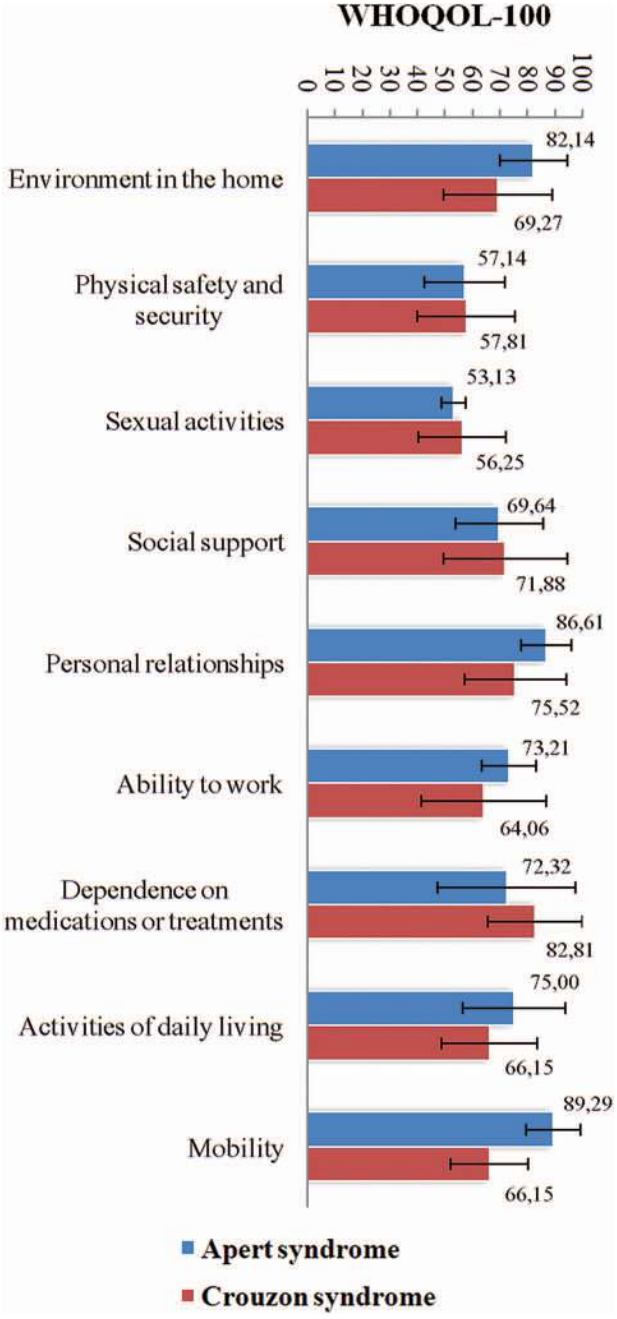

Fig. 4. Quality of life of Apert or Crouzon syndromes patients based on World Health Organization Quality of Life-100 (*WHOQOL-100*) facets. Apert patients showed significantly higher scores in the home environment ($p = 0.046$) and mobility ($p = 0.037$) than Crouzon patients.

Sarimski[9] interviewed parents of 41 patients with Apert syndrome and showed that despite their handicaps, the patients functioned well socially. The major problems relied on the parents' acceptance of their child's appearance and behavioral inadequacies, parental low self-esteem, and depression.[9] Although we did not measure the parents' quality of life, it seems that it is significantly more affected than their own children's perception of quality of life. A further study that compares the quality of life of children born with Apert and Crouzon with their parents' quality of life will elucidate this interesting subject. Anecdotally, the parental fear for their children's future, without the immense support of these children, requires an impact on negative parental feelings such as hopelessness and depression. On the other hand, their children or adults with syndromic craniosynostosis, especially Apert syndrome, seem to

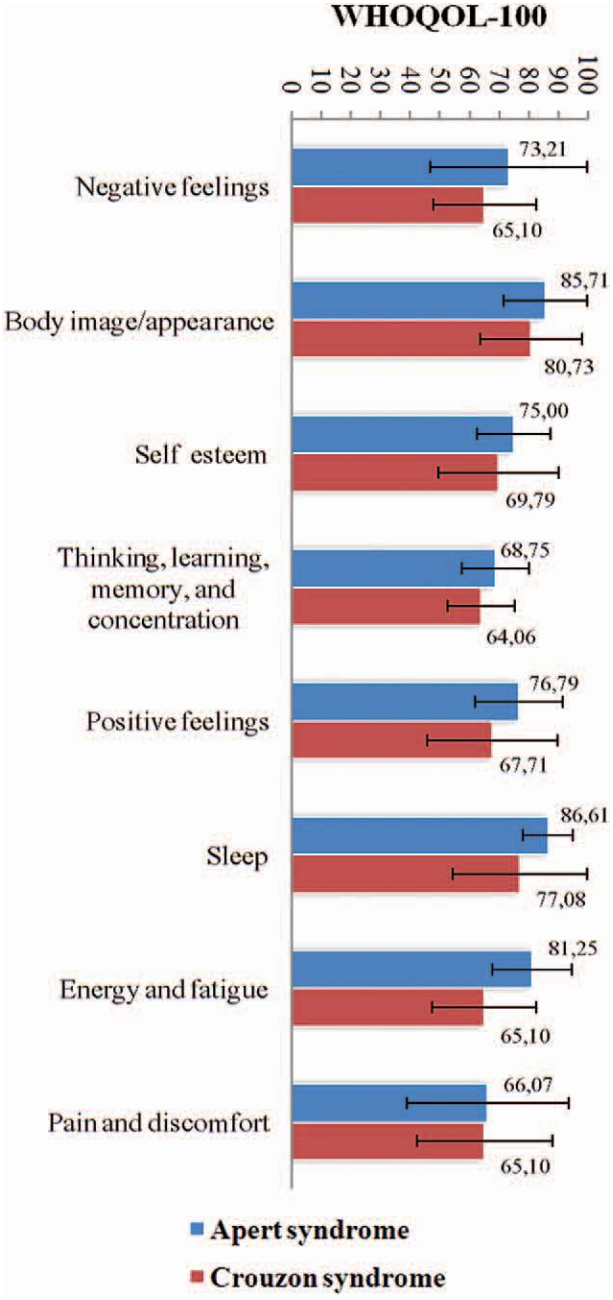

Fig. 5. Quality of life of Apert or Crouzon syndromes patients based on World Health Organization Quality of Life-100 (*WHOQOL-100*) facets. Apert patients showed significantly higher scores in energy and fatigue ($p = 0.05$) than Crouzon patients.

be less attentive to subtle insults that involve more elaborative thinking. This behavioral characteristic promotes their ability to positively rate their quality of life, bringing a more optimistic understanding of their overall condition.

Rationally, one can initially assume that patients with Crouzon syndrome, who undergo significantly fewer operations than Apert patients, would show higher quality-of-life scores. To the best of our knowledge, this is the first study to compare quality of life in Apert and Crouzon syndromes while adhering to a multidisciplinary approach and a management protocol. Interestingly, in opposition to our initial hypothesis, quality of life in the Apert syndrome patient does not differ from that of Crouzon syndrome patients. Our data show that Apert syndrome patients presented higher scores in 17 facets (68 percent) and in five domains (83.33 percent) compared with Crouzon syndrome patients. Since Da Costa et al.[5] reported an intelligence quotient of 70 for Apert patients and 92.3 for Crouzon patients, we hypothesized that higher levels of intelligence in Crouzon syndrome bring the patient complete awareness of his or her physical limitations (breathing, visual, and hearing impairments) and the stigma, teasing, and bullying from school classmates that these patients have to deal with during their daily routine. On the other hand, the lower levels of intelligence in Apert syndrome may interfere with patients' ability to fully understand their overall limitations but positively influence their own perception of their quality of life. These aspects may partly explain why Apert patients reported significantly higher scores on mobility than Crouzon patients. Moreover, since early craniofacial interventions allow for brain growth that may result in greater intellectual development,[18] the focus should be on early intervention in these Apert patients, to allow for neuropsychological development. In addition, early lower and upper limb reconstruction allows for acquisition of the motor abilities necessary to manipulate objects and gain self-confidence and independence,[20] as exemplified in Video**, Supplemental Digital Content 1,** which demonstrates the motor abilities of two 3-year-old children with Apert syndrome, ***http://links.lww.com/PRS/A938***. The parents of the first patient were told elsewhere that the hand reconstruction should only be done when the child reached 9 years of age, and the second patient was referred to our unit just after birth and adhered to a strict treatment protocol. Behavior characteristics by means of feeling of motivation, curiosity, persistence, and sense of achievement are different between the two children. The quality of life of syndromic patients may be significantly diminished by the absence of early reconstructive surgical procedures.

The limitation of this study is that it relied on the evaluation of patients, who had been receiving the constant support of a multidisciplinary team, who had already undergone the major craniofacial procedures of either monobloc craniofacial

Video. Supplemental digital content 1 demonstrates the motor abilities of two 3-year-old children with Apert syndrome, ***http://links.lww.com/PRS/A938***. The parents of the first patient were told elsewhere that the hand reconstruction should only be done when the child reached 9 years of age, and the second patient was referred to our unit just after birth and adhered to a strict treatment protocol. Behavior characteristics by means of feeling of motivation, curiosity, persistence, and sense of achievement are different between the two children. The quality of life of syndromic patients may be significantly diminished by the lack of early reconstructive surgical procedures.

advancement or subcranial Le Fort III and upper and lower limb reconstruction, and who had acquired the necessary psychological repertoire to respond to any eventual adverse behavior from their peers.

There are health-related quality-of-life instruments designed to specifically assess children with punctual age or to be completed by their proxy.[27,43,47] The caveat of using these instruments is that the proxy evaluation tends not to correlate with the patient's own evaluation.[48–50] In addition, these instruments limit the comparison of patients with similar clinical features (that somehow linked them in the same syndromic clinical spectrum) and with distinct age. In our study, we compared patients with different ages because the World Health Organization Quality of Life-100 questionnaire does not restrict it. Warschausky et al.[47] also compared patients with different craniofacial syndromes and with different ages, since the instruments they used allowed this. Interestingly, age has shown no influence on quality of life.[27]

By excluding those Apert patients with moderate and profound delay ($n = 2$), we did not evaluate patients who could not minimally analyze their quality of life based on their own judgment and perception and ended up selecting the highest-functioning Apert patients. The selection bias seen in our study can also be found in previous studies about health-related quality of life in syndromic craniosynostosis.[27,43] The complex process of questionnaire validation used in these studies,[27,43] as with others performed with the World Health Organization Quality of Life-100 questionnaire,[32–34,40–42] considered the need to exclude those patients who are not eligible to fully respond to it and did not nullify the final result obtained by it. In an attempt to overcome the selection bias issue, de Jong et al.[27] included the proxy responses on behalf of patients' relatives. However, these evaluations done by parents did not correlate with the patients' judgment, and a measurement error occurred.[48–50] In this context, patient-reported instruments to specifically categorize quality of life in patients with craniofacial syndrome and severe handicap are needed in the literature.

It is likely that random patients who did not adhere to a strict multidisciplinary protocol (as shown in **Video, Supplemental Digital Content 1**, ***http://links.lww.com/PRS/A938***) or untreated patients with either Crouzon or Apert syndromes could decrease the average scores obtained from responses to a patient-reported outcome quality-of-life questionnaire.

The individual's perception of quality of life is a dynamic process, meaning that the judgment of quality of life may vary during exponential problematic home environment or other major distress,[51] which was not the situation in our cohort. After the patients had completed the World Health Organization Quality of Life-100 instrument and followed the instructions of the questionnaire, we did not personally interview our patients to collect

Table 1. Quality of Life of Apert or Crouzon Syndromes Patients Based on World Health Organization Quality of Life-100 Domains

	WHOQOL-100 Domains					
Patients	**Physical Ability (%)**	**Psychological (%)**	**Independence Level (%)**	**Social Relations (%)**	**Environment (%)**	**Spiritual (%)**
Apert syndrome	77.98	75.89	77.46	75.60	68.30	77.68
Crouzon syndrome	69.10	69.48	69.79	69.70	65.36	79.17
p	0.271	0.253	0.251	0.610	0.554	0.898

WHOQOL-100, World Health Organization Quality of Life-100.

any further detailed information to complement our data. Although this may represent an inherent limitation of the questionnaire, there is no recommendation in the literature on how to accurately deviate from the validated application manner of the questionnaire nor any other questionnaire on quality of life.[52] However, the paucity of further detailed individual information, in addition to our reduced sample size and the lack of comparison to normative scores from the general population, may have biased some of our results.

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PATIENT CONSENT

Patients or parents or guardians provided written consent for the use of the patients' images.

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