The Influence of Genetic Syndromes on the Algorithm of Cleft Lip and Palate Repair – A Retrospective Study

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Abstract

Introduction: This study aimed to determine if the treatment algorithm used for nonsyndromic cleft patients required alteration to manage syndromic cleft lip and/or palate patients. **Methods:** The records of patients managed by the Pécs Cleft Team between January 1999 and December 2015 were analyzed retrospectively. The sources of the data included clinical and genetic records. **Results:** A total of 607 patients were managed by the cleft team during the study. Sixteen patients (2.6%) were noted to be afflicted with a particular identifiable syndrome. Seven different genetic syndromes and one sequence were present in the study. The Pierre Robin sequence occurred most often, comprising 50% of the cohort. The treatment algorithm used in managing nonsyndromic clefts required modification in 13 of the 16 syndromic patients. **Discussion:** The presence of a genetic syndrome may notably affect the treatment algorithm in children born with cleft lip and/or palate. The surgical treatment of certain associated anomalies has by necessity, priority over the timing of the reconstruction of the cleft lip and/or cleft palate in syndromic patients.

Keywords: Child, cleft lip, cleft palate, syndrome, treatment timing

INTRODUCTION

Cleft lip and/or cleft palate (CLP) are common developmental anomalies.^[1] In general, the worldwide incidence of clefts is estimated to be between 1 and 2.21 cases per 1000 live births.^[1] In most cases, CLP occurs as an isolated anomaly. However, the association of CLP with genetic syndromes, the so-called syndromic cleft lip and palate (SCLP), has been described previously in the seventies.^[2] At that time, only 154 cleft-related syndromes were known in contrast to the well over 500 syndromes recognized in the literature today.^[3] SCLP patients represent between 10% and 30% of CLP cases, according to past and current publications.^[3-5]

The aim of this clinical study was to identify syndromic cleft patients and evaluate how their genetic syndrome influenced the timing of the algorithm in the treatment of CLP. The study was conducted on patients managed by the Pécs Cleft Team (PCT) between January 1999 and December 2015.

METHODS

A study of nonsyndromic and syndromic cleft patients managed and followed by the PCT was conducted over the 16 years between January 1999 and December 2015. Detailed clinical documentation of all patients, including genetic and epidemiological data, was required for inclusion in the study. The data were collected retrospectively without personal identifying details. At the time of the data collection, permission from the regional ethical committee was not deemed to be obligatory because of the retrospective nature of the study. Special permission was obtained and granted for data collection from the Hungarian Congenital Abnormality Registry (HCAR). The

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Ethics Committee of the University of Pécs waived the need for ethics approval and the need to obtain consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this study. The reason for this waiver was the retrospective nature of this study and the anonymized nature of the data used in the study. All procedures performed in the study were conducted in accordance with the ethics standards given in the 1964 Declaration of Helsinki, as revised in 2013.

Special emphasis was placed on the syndromic features of the patients and their associated anomalies. The type and timing of the surgeries or interventions unrelated to the clefts were listed and categorized. The timing of the cleft lip and/or cleft palate repair was recorded as well, and was compared with the algorithm used for nonsyndromic cleft patients. The Online Mendelian Inheritance in Man database^[6] was used to identify the genetic syndromes. Epidemiological data were obtained from the HCAR. The study used descriptive statistics consisting of means and percentages of the presenting syndromes and participants of the study, which were calculated and used along with standard deviations in the data analysis.

RESULTS

Among the 607 CLP patients, 25 children (4.1%) had associated anomalies noted during the study period. Sixteen (2.6%) of

the 607 CLP patients were found to be SCLP cases. A total of seven different genetic syndromes and one sequence were identified in this cohort [Figure 1a and b].

Pierre Robin sequence (PRS) comprised 50% of all cases. Ten patients (60%) were boys and six (40%) were girls of the SCLP group. The majority of the SCLP patients had cleft palate only, $n = 13$ (81%) [Figure 2]. The other syndromes observed in the cohort included: Smith-Lemli-Opitz syndrome, Dandy-Walker syndrome, DiGeorge syndrome, Ectrodactyly-ectodermal dysplasia-clefting syndrome, Treacher Collins syndrome, Turner syndrome, and Weissenbacher-Zweymüller syndrome.

The algorithm used by the PCT had to be modified for most of the SCLP patients ($n = 13$, 81%). The modifications were necessary due to the nature and needs of the given syndrome. This was true in all SCLP cases, except for one patient. The timing of the cleft repair procedure in the SCLP cohort is illustrated in Figure 3.

The authors observed notable delays in the timing of the palate repair in SCLP patients. In two SCLP patients, the palatoplasty procedure was completed much later, at 4 years of age. In addition, 15 patients underwent additional surgeries due to the presence of the syndromes and associated medical conditions [Figure 4]. These operations had of necessity priority over the repair of the CLP deformities. Tracheostomies were needed in three patients with PRS.

Secondary operations for CLP were required in six patients (37.5%). Speech improvement operations or pharyngoplasty and tympanostomy tube placements were the most common secondary operations. These procedures were mainly required in patients with PRS [Figure 5].

DISCUSSION

Treating SCLP patients is by nature, more complex than treating nonsyndromic cleft patients. Syndromic patients require more attention and support for their multiple potential special needs from both the family and the health care facility, including the cleft teams.^[1,7-11]

Figure 1: (a) The distribution of the seven genetic syndromes and one sequence present in the cohort. (b) Number of individuals in each group

Figure 2: The distribution of cleft type in syndromic patients

Figure 3: The timing of the cleft repair surgery for syndromic patients. Vertical lines in bold (1 and 2) represent the usual timing of the cleft repair surgeries carried out by the Pécs Cleft Team. Patients 1–16 are grouped according to the types of syndromes

Figure 4: The distribution of additional surgeries for the affected organ system (s) for syndromic patients

Figure 5: Types of secondary ancillary operations carried out on syndromic cleft patients

The percentage of the SCLP patients managed by the PCT was 2.6% during the study. This number is below the 10% and 30% prevalence described in the literature.^[3-5,12,13] On the other hand, the prevalence of PRS in the SCLP cohort was similar to the literature, according to the data obtained from the HCAR. In contrast, Smith-Lemli-Opitz, Dandy-Walker syndrome, and Turner syndrome were underrepresented in this SCLP cohort. The under-diagnosis and/or reporting of cases could be responsible for their low prevalence.

Interestingly, two very rare syndromes both Ectrodactyly-ectodermal dysplasia-clefting syndrome and Weissenbacher-Zweymüller syndrome were present in the syndromic cohort.^[14-16] A center for rare congenital diseases was subsequently established in Pécs during the latter half of the study period, in 2009, which may explain the more current appearance and reporting of these rare syndromes.

The cleft team needed to modify the treatment algorithm for CLP in the majority (81%) of the SCLP patients. One example of these alterations is the delay of the primary cleft repair operations. The main causes of the delay in palatoplasty for PRS patients were airway issues and feeding problems. In other patients, cardiorespiratory and urogenital interventions had priority over the cleft surgeries. Upper respiratory infections also caused a delay in the timing of the primary cleft operations in some cases [Figures 3 and 4].

The high rate (37.5%) of the secondary operations such as speech improvement surgery and ancillary procedures such as placement of tympanostomy tubes for the SCLP patients is in accordance with the literature.^[7,11,17-19]

The authors have noted velopharyngeal insufficiency and speech problems as more common conditions in SCLP patients, especially those patients with PRS. This explains the high rate of pharyngoplasties and tympanostomies in these patients.^[7,17-19] The author's findings support these observations. In some previous studies, however, no differences were found between the secondary operations for nonsyndromic patients and patients with PRS.^[20]

CONCLUSION

The presence of a genetic syndrome noticeably altered the treatment algorithm of the PCT in the majority of children born with SCLP (81%) compared to nonsyndromic CLP patients. The surgical treatment of the associated anomalies has priority over the timing of the reconstruction of the cleft lip and palate in a number of syndromic patients. Cleft palate only and velopharyngeal insufficiency were more common in the syndromic group. Secondary operations for clefts were needed in greater numbers in SCLP patients than in nonsyndromic patients. With improvements in pediatric care and better recognition of the milder phenotypes, the number of future SCLP patients is likely to increase. Syndromic patients

will likely require further flexible modifications of the cleft treatment timing algorithm.

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Conflicts of interest

Dr. George Kalman Sandor was associated as a section editor of this journal and this manuscript was subject to this journal's standard review procedures, with this peer review handled independently of this section editor and their research group.

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