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Additional diagnoses in children with cleft lip and palate up to five years of age

Ellen Aspelin^{a,b}, Måns Cornefjord^{a,b}, Kristina Klintö^{c,d} (D) and Magnus Becker^{a,b}

^aDepartment of Clinical Sciences in Malmö, Lund University, Lund, Sweden; ^bDepartment of Plastic and Reconstructive Surgery, Skåne University Hospital, Malmö, Sweden; ^cDepartment of Clinical Sciences in Lund, Lund University, Lund, Sweden; ^dDepartment of Otorhinolaryngology, Skåne University Hospital, Malmö, Sweden

ABSTRACT

Cleft lip and palate (CL/P) is the most common congenital craniofacial malformation and is often associated with additional diagnoses. The purpose of this study was to explore the cumulative five-year incidence of additional diagnoses for patients with cleft lip and palate. Further aims were, type of cleft and type of additional diagnose and to validate CLP registry data on additional diagnoses. Data from the CLP registry regarding children with CL/P in the Southern Health Care Region were retrieved and based on the registry, participants were selected. A review of medical records of participants born 2006–2016 was performed and data regarding participant characteristics and additional diagnoses were collected. Of the 250 participants included in the review of medical records, 90 participants (36%) had an additional diagnosis. Of the total number of identified additional diagnoses (n = 137), cardiovascular system (20.4%) and extremities and skeletal system (17.5%) were the most prevalent categories. The comparison between medical records and the CLP registry of all children showed a 14.4 percentage points higher incidence of additional diagnoses in the medical records. Roughly every third child received an additional diagnosis and diagnoses related to the cardiovascular system were the most frequent. This study also shows that additional diagnoses were under-reported in the CLP registry. Future research is necessary to strengthen associations of additional diagnoses to CL/P.

ARTICLE HISTORY

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KEYWORDS

Cleft lip and palate; CLP registry; additional diagnoses

Introduction

Cleft lip and palate (CL/P) is the most common congenital craniofacial malformation [1]. Out of 1400 live births in Sweden, approximately two children are born with this malformation every year [2]. CL/P shows significant variation in its clinical presentation and its embryological background is complex. The cause of the condition is not fully understood, and there are several potential explanations for its occurrence. It development seems to be subject to a combination of genetics [3], environment [4], and lifestyle of the parents [4]. Depending on the nature of the cleft, it can affect structures such as the lip, palate and alveolus to different extents and in different combinations. It in turn, this affects appearance and functions such as hearing [5,6] and speech [7]. The main treatment for CL/P in Sweden is surgical intervention in combination with follow-up and treatment by one of six regional multidisciplinary CL/P treatment teams [8].

It is known that CL/P is often associated with additional diagnoses such as congenital heart defects [9], Pierre Robin sequence [10,11] and 22q11-syndrome [12]. It has been recognised that it is more common to have a single rather than several additional diagnoses to CL/P [12–14]. Today, there are over 400 identified syndromes for which different types of clefts can occur [12]. Previous studies regarding the incidence of diagnoses associated with CL/P present significantly different results [9,12,15]. In 1985, a retrospective study including 1000 participants showed an incidence of associated malformations of 63.4% among children with CL/P [9], compared with a prospective Swedish study from 1997 including 616 participants that presented an incidence of 21% [12]. A larger, European registry study including 5449 children with CL/P [15] was published in 2007 and was based on the EUROCAT network, including 14 European countries and 23 registers; this study estimated that 29.2% of the children had an associated defect [15]. Research in the field generally meets difficulties regarding selection of participants, sample size, inclusion/exclusion criteria for associated diagnoses, and length of time after birth for which diagnoses are studied [16]. There is occasionally a delay in some additional diagnose, as symptoms can be very subtle, which leads to the diagnose not being identified until later in life [17].

Since 2009, all children with CL/P in Sweden have been offered the opportunity to participate in the national quality registry for patients born with CL/P (CLP registry). Included in the registry is data from CL/P centres regarding, for example, the type of cleft and prevalence of Pierre Robin sequence, syndromes, and other deformities [18,19].

The primary aim of this study was to explore the cumulative five-year incidence of additional diagnoses presented in children with CL/P. Further aims were to investigate the relationship between type of cleft and type of additional diagnosis, and to validate CLP registry data on additional diagnoses.

Methods

Selection of participants

The participants were born from 2006 to 2016. The guardians of the children had approved the registration of their children in the

CONTACT Magnus Becker 🖾 magnus.becker@med.lu.se 🖃 Department of Clinical Sciences in Malmö, Lund University, Lund, Sweden

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CLP registry at previous visits to the Department of Plastic and Reconstructive Surgery at Skåne University Hospital. All guardians of children in the CLP registry who were born with CL/P in the Southern Health Care Region during the specified period were asked to provide consent for participation in the study, and only the children with consenting guardians were included in the study (hereinafter referred to as participants).

Selection of variables

The selection of variables aimed to include clinically relevant diagnoses associated with CL/P [9,12-15]. Only diagnoses coded according to the Swedish National Board of Health and Welfare's classification of health intervention or confirmed malformations [20] were included. It was not considered sufficient to suspect and include a syndrome based on the fact that a child had multiple malformations alone. Excluded diagnoses were transient infections, allergies, refractive errors, childbirth complications, physiological heart wheezing, and hypertrophy of the tonsils and adenoids. The exclusion was due to the fact that it was hard to evaluate the frequencies of these diagnoses among children with CL/P without knowledge about the prevalence of these common diagnoses within the paediatric population in general [9,12-15]. Additional excluded variables were secretory media otitis, speech deficiencies, malocclusions, and dental anomalies, since these are common and well-known associated diagnoses among children with CL/P [6,12,21].

The classification of clefts was based on diagnosis codes according to the ICD-10 [22]. The cleft diagnoses were then gathered into four bigger groups depending on the affected structure.

Variable description

The CLP registry includes children from all Swedish Health Care Regions, and among them the Southern Health Care Region, which includes the Health Care Region of Skåne, southern Halland, Kronoberg and Blekinge. Southern Halland, Kronoberg and Blekinge all have different systems for medical records to the Health Care Region of Skåne. Therefore, for participants living outside of Skåne, only medical records made in conjunction with visits to the CL/P team in Malmö could be reviewed. Any additional diagnosis was categorised based on a structure or system with an overall title, and then subdivided into specific parts of the structures or systems.

CLP registry and review of medical records

Data regarding occurrence of the Pierre Robin sequence, syndromes and other deformities were retrieved from the CLP registry for all registered children in the Southern Health Care Region and were compared with the results from the review of medical records of those who had given consent for the study. The medical records of the participants were then reviewed for the chosen variables. The variables for general background characteristics were sex, age, whether they lived in Skåne, and whether they were born abroad. The variables describing participant medical history were the type of cleft, and additional diagnoses received at birth and up to the age of five years. Information was collected from the medical records during visits to clinics in the Health Care Region of Skåne. Participants with a syndrome or sequence were only included in the results once. A deformity that was significant for a specific syndrome or sequence was included under the term syndrome or sequence and did not get noted as a deformity. In that case, these participants would have been included twice.

Statistics

Statistical analysis of the data was performed using IBM SPSS Statistics Version 28.0.0.0. The results are presented with descriptive statistics, using frequencies, median, range and percentage.

Ethics

The study was approved by the Ethics Review Authority in Sweden (reference no. 2021-05893-01). In order to review the participants' medical records, approval from the consultation group for quality registries, care databases and preparation in the Skåne region (KVB) was obtained. The participants' guardians received written information by mail regarding the purpose of the study, voluntariness, management of sensitive personal data, GDPR and future profit. The information from each child was pseudonymized by giving them a personal id number.

Results

A total of 436 children with CL/P were born in the Southern Health Care Region of Sweden and registered in the CLP registry during the period 2006–2016. Informed consent was obtained for 250 children (Figure 1). The characteristics of the participants are shown in Table 1. The numbers of participants in the cleft lip (CL), cleft palate (CP) and unilateral cleft lip and palate (UCLP) groups

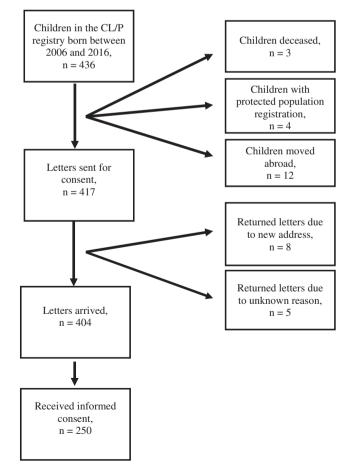


Figure 1. Flow chart of participant selection. Returned letters were letters that never arrived to the guardians of the child.

were similar. The group with bilateral cleft lip and palate (BCLP) was smaller (Table 1).

Additional diagnoses

Based on the review of medical records, a total of 67 (28.8%) participants were diagnosed with a single additional diagnosis, and 23 (9.2%) participants were diagnosed with two or more additional diagnoses (Figure 2). Separate diagnoses included in a syndrome or sequence were excluded. Among the 250 included participants, a total of 137 additional diagnoses were identified, since one type of additional diagnosis could be identified in several children (Table 2). The two categories identified most frequently were diagnoses associated with the cardiovascular system, and extremities and skeletal system, making up 20.4% and 17.5% of the total number of identified diagnoses, respectively (Figure 3). The most common additional diagnoses that were withdrawn were corrected heart defects (Table 2).

Table 1. Characteristics of participants in the study and children in the CLP registry, with data presented as frequency and percentage. Information on whether a child lived in Skåne could only be obtained from the medical records.

Participant characteristics, n (%)	Participants in the study, $n = 250$	Children in the CLP registry, $n = 436$
Male, n (%)	164 (65.6)	280 (64.2)
Female, n (%)	86 (34.4)	156 (35.8)
Born abroad, n (%)	42 (16.8)	62 (14.2)
Lived in Skåne, (%)	191 (76.4)	
Type of cleft, n (%)		
Cleft palate	67 (26.8)	136 (31.2)
Male	39 (58.2)	67 (49.3)
Female	28 (41.8)	69 (50.7)
Cleft lip	67 (26.8)	126 (28.9)
Male	44 (65.6)	85 (67.5)
Female	23 (34.3)	41 (32.5)
Bilateral cleft lip and palate	43 (17.2)	65 (14.9)
Male	31 (72.1)	42 (64.6)
Female	12 (27.9)	23 (35.4)
Unilateral cleft lip and palate	73 (29.2)	109 (25.0)
Male	52 (71.2)	80 (73.4)
Female	21 (28.8)	29 (26.6)

Type of cleft and cumulative five-year incidence of additional diagnoses

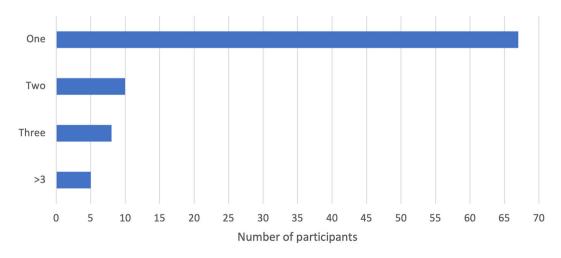
In the CL group, the highest number of additional diagnoses were found within the cardiovascular system category. Within the CP group, the highest number of additional diagnoses were found within the sequences, and extremities and skeletal system categories. In the BCLP group, the highest number of additional diagnoses were identified within the extremities and skeletal system; and ears, nose or throat categories. For the UCLP group, the highest number of additional diagnoses were within the cardiovascular system category.

Comparison with data in the CLP registry

A comparison between data on additional diagnoses in the CL/P registry and in the medical records is presented in Table 3. It was found that, for four participants, the Pierre Robin sequence diagnosis had not been registered in the CLP registry. Five participants were diagnosed with a syndrome according to the medical records, but this had not been registered in the CLP registry. Furthermore, 44 participants were diagnosed with another deformity according to the medical records, but was registered in the CLP registry.

Discussion

In this study, the cumulative five-year incidence of additional diagnoses among children with CL/P was investigated. We also investigated potential relationship between the type of additional diagnosis and the type of cleft. The study also functioned as validation of data on additional diagnoses in the CLP registry. When reviewing the medical records of the participants, the highest number of additional diagnoses were identified within the categories cardiovascular system, and extremities and skeletal system. Out of 137 additional diagnose, s a total of 69 additional diagnoses were established in direct connection with birth, and 68 additional diagnoses were received after birth and before the age of five. Sixty-seven of the 90 participants with an additional diagnosis had a single additional diagnosis.



Number of additional diagnoses

Figure 2. Number of additional diagnoses in individuals among the 250 participants, when diagnoses related to syndromes and sequences were excluded.

Number of additional diagnoses

Table 2. Identified syndromes, sequences, and other additional diagnoses in the medical records among the 250 participants, with separate diagnoses included in a syndrome or sequence excluded.[AQ2]

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Table 2. Continued.

Clinical variables, n (%)	Participants in the study, N = 250	Age in years at diagnosis, median (min–max)	Age in years at withdrawn diagnosis, median (min–max)
Hydroureter	2 (0.8)		
Micropenis	1 (0.4)		
Bilateral retention testis	1 (0.4)		
Fimosis	1 (0.4)		
Hydrocele	1 (0.4)		
Hypospadia	1 (0.4)		
Ears, nose, throat, n (%)	13 (5.2)	0.5 (4)	
Preaurical skin tag	3 (1.2)		
Auricular malformation	3 (1.2)		
Sensorineural hearing loss	3 (1.2)		
Swallowing difficulties	2 (0.8)		
Low set ears	1 (0.4)		
Laryngomalacia	1 (0.4)		
Endocrine system, n (%)	2 (0.8)	1 (0)	
Diabetes insipidus	1 (0.4)		
Hypopituitarism	1 (0.4)		
Respiratory system, n (%)	1 (0.4)	0 (0)	
Cystic fibrosis	1 (0.4)		
Dermatology, n (%)	10 (4.0)	0 (1)	
Salmon patch	4 (1.6)		
Hemangioma	5 (2.0)		
Dermatofibroma	1 (0.4)		

Percentage of each category of all additional diagnoses

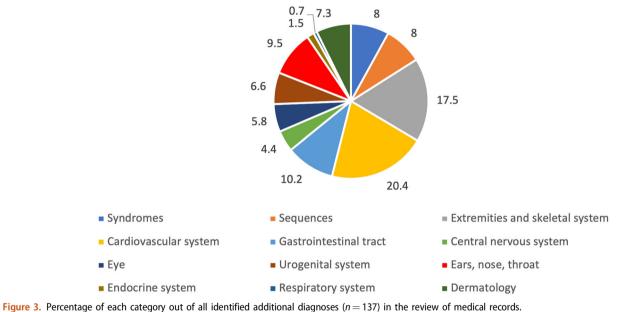


Table 3. Cases of Pierre Robin sequence, syndrome and other deformities in the CLP registry and from the review of medical records of the 250 participants, presented as frequency and percentage. All separate diagnoses for each participant with a syndrome were excluded.

Categories, n (%)	Data for all children in the CLP registry, $n = 436$	Data for study participants, $n = 250$, from the CLP registry	Data for study participants, $n = 250$, from medical records
Pierre Robin	14 (3.2)	7 (2.8)	11 (4.4)
Syndrome	19 (4.4)	8 (3.2)	11 (4.4)
Other deformity	60 (13.8)	32 (12.8)	68 (27.2)
Total	93 (21.3)	47 (18.8)	90 (36.0)

Previous published studies have mainly investigated the total incidence of diagnoses associated with CL/P [9,12–15]. The reported total incidence in these studies varies from 21% to 63. 4%. In this study, the total incidence of additional diagnoses was 36%, which is similar to the registry studies by Beriaghi et al. [13]

and Calzolari et al. [15], who reported an incidence of 32.3% and 29.2%, respectively. The results in the present study, showing a higher cumulative five-year incidence of associated diagnoses, could partially be explained by the fact that we scrutinized the medical records and had wide inclusion criteria for diagnoses.

Generally, there were inconsistencies in the designs of previous studies, which could partly be explained by different inclusion and exclusion criteria [9,12–15].

In accordance with previous studies, the present study showed that diagnoses of the cardiovascular system, and extremities and skeletal system were the most frequent associated diagnoses [9,12,13]. In the review of the medical records, the number of additional diagnoses almost doubled from just after birth until the age of five years. This reinforces the importance of frequent follow-ups and should be taken into consideration when providing information for parents regarding when additional diagnoses can be detected. For the more extensive clefts, the BCLP and UCLP groups, higher rates of additional diagnoses were registered later than in direct connection with birth, whereas in the CP group, the majority of all additional diagnoses were received in direct connection with birth. Knowledge of when specific additional diagnoses are established can improve the detection of subtle signs and enable diagnosis at an earlier age. The results regarding at what age additional diagnoses were withdrawn were inconsistent and further research is necessary on this area.

In this study, the prevalence of the Pierre Robin sequence registered in medical records was higher than that registered in the CLP registry. Overreporting in medical records is probably more common when a child has a small chin and isolated CP, due to the difficulties in distinguishing between Pierre Robin sequence and isolated CP [23]. The high prevalence of Pierre Robin sequence within the CP group can be explained by its aetiology [10,11]. No syndromes were found within the CL group, which supports the thesis that a more extensive cleft seems to be associated with a higher risk of additional diagnoses [15].

The high prevalence of additional diagnoses has implications for the genetic counselling offered and the type of information that may be given to guardians. However, by the methods used in this retrospective study, it was not possible to provide statistically verifiable results. To gain a deeper understanding of the relationships between these factors, a prospective study that follows the children from birth until they are adults may be a way forward. Ideally, the follow-up would be undertaken similarly for all children, and with precise inclusion and exclusion criteria from the commencement of the study. Another possible option for a prospective study would be to explore the co-occurrence between additional diagnoses and CL/P, as there has been limited research of this nature [24].

It is beneficial that this study can also serve as a validation of data in the Swedish CLP registry. It is of high importance to validate the data in the CLP registry, since it is the basis of improvement for the care for children with CL/P [18]. There were notable discrepancies between registrations of additional diagnoses in the CLP registry of the included children and that retrieved during the review of medical records of the same children. A possible reason for the differences could be varying inclusion criteria for an additional diagnosis, since each registration of data in the CLP registry is due to individual considerations by the registering medical personnel. This highlights the importance of a well-structured guide for registration of data, as the registration in the CLP registry is also dependent on all medical personnel remembering and having the knowledge of how to perform registration in the CLP registry. To be able to use large registries for open comparisons, research and statistics, it is crucial that they are up to date and correctly filled in. In order to motivate clinical geneticists to perform genetic tests on children with CL/P, well-developed grounds are necessary. If there is an interest from the guardians,

a diagnosis of a syndrome may help them to better understand their child's needs.

Although the study was retrospective, required consent, and had a set age limit, it was thorough and had wide inclusion and exclusion criteria. The wide inclusion criteria regarding additional diagnoses in this study might contribute to increased knowledge regarding which additional diagnoses may be associated with CL/ P. The knowledge of the high percentage of additional diagnoses, and especially heart defects [12], in children with CL/P should be taken into consideration before planning surgical procedures, as numerous severe heart defects can affect the child's condition.

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Author contributions

Ellen Aspelin, main researcher involved in design, planning, execution, and writing.

- Måns Cornefjord, involved in writing and analyzing results. Kristina Klintö, involved in execution and writing.
- Magnus Becker, supervisor involved in design, planning, execution, and writing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Kristina Klintö (D) http://orcid.org/0000-0002-7044-9386

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