Prevalence and Type of Associated Syndromes in Patients with Cleft Lip and Cleft Palate Who Received the Treatment in Tawanchai Center until 4-5 Years of Age

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Background: *Understanding the genetic etiologies of cleft lip and palate (CLP) is important for improved prevention, treatment, and prognosis for patients affected by CLP.*
Objective: *To report the prevalence and the type of associated syndromes in Northeastern Thai patients with CLP.*
Material and Method: *A retrospective study of 123 cleft lip/palate children aged 4-5 years was carried out at the Tawanchai Cleft Center, Khon Kaen University during the period from October to December 2011. Data were collected by reviewing the patient's medical records.*
Results: *Seventeen (14%) of the 123 children had multiple malformations and five (4%) of these children had associated syndromes. Syndromes were identified in 5 (29%) of the 17 children who had associated malformations. The syndromes were Apert, Cleft lip/palate-ectodermal dysplasia, Kabuki, Oculo-Auriculo-Vertebral Spectrum, and Velocardiofacial syndrome.*
Conclusion: *Recognition of the associated syndrome in a patient with CLP is essential to assess the problem of the patient, provide necessary treatment and the appropriate methodology of prevention.*

Keywords: *Children, Cleft lip, Cleft palate, Syndrome*

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Cleft lip (CL) and cleft palate (CP) are frequent congenital malformations of the head and neck[1,2] and have complex etiologies with environmental and genetic factors[3,4]. The birth prevalence of cleft lip and cleft palate (CLP) varies between 0.8 and 2.5 cases per 1,000 live births[1,5-7] according to population, ethnicity, and sex and is high among American Indian and Asian children[5-7]. CLP can occur as an isolated problem or may be associated with a syndrome[3,4].

Understanding the genetic etiologies of CLP is important for improved prevention, treatment, and prognosis for patients affected by CLP. Information of the genetics underlying CLP is gathered partly from the knowledge of the syndromic form of this disease[3,4]. Since, there are few data on the reported prevalence and type of syndrome associated with CLP found among the Thai population[8,9], the authors reported the prevalence and the type of associated syndromes in Northeastern Thai patients with cleft lip and palate who received follow-up care by the multi-disciplinary teams at the Tawanchai cleft center until 4-5 years of age.

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Material and Method

From October to December 2011, 123 CLP children received continuous multidisciplinary treatment and follow-up care until 4-5 years of age at the Tawanchai Cleft Center, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University (KKU)[1,10]. The method of the continuous multidisciplinary care has been reported previously[1,10]. In brief, of the 123 children, 120 (98%) cases had operations at Tawanchai Center[1] and 38 (31%) cases came to receive treatment

at less than 1 month of age. The average number of follow-up visits of the study patients was 18.4 (range, 10-220) visits[10]. However, the present report was focusing on the prevalence and type of associated syndromes in CLP children. The clinical data were retrospectively collected including: patient's sex, age, type of cleft and syndromes associated with CLP. Each child underwent a thorough clinical examination by a pediatrician. Because of variation in the timing of the apparent associated syndrome, follow-up until the child is four or five years of age is needed[1,10]. CLP children with associated malformations were divided into three groups: syndromes, malformation complexes and sequences. Syndromes were diagnosed in cleft patients on the basis of presence of additional clinical features, cognitive abnormalities and relevant investigations. A pediatrician and a geneticist classified the type of associated syndrome in this patient group. The recognized syndrome, in which CLP is a primary feature, has been searched in the National Center for Biotechnology database to determine the causation, including: mutation of genetic locus, chromosomal abnormality, or environmental causes. However, facial clefts found in two children were grouped as malformation complexes. Moreover, the most frequent malformation sequence found in this patient group was the Pierre Robin sequence found in two children and the second most common was Amniotic bands sequence found in one child.

Fluorescence in situ hybridization (FISH) testing for 22q11.2 deletion is performed in a child who was suspected of having Velocardiofacial syndrome. The children, who were considered to have congenital heart disease, were examined in detail by pediatric cardiologists.

The present study was approved by the Human Research Ethics Committee, Khon Kaen University, with the approval number of HE541281.

Results

There were 123 patients in this study group with 70 (57%) boys and 53 (43%) girls. Of these patients, 74 (60%) patients had both cleft lip and palate, 30 (24%) patients had isolated cleft lip, and 19 (16%) cases had isolated cleft palate. Twenty (16%) cases were originally from Khon Kaen province.

Prevalence of associated syndromes

Seventeen (14%) of the 123 children had associated malformations and five (4%) of these children had associated syndromes. Syndromes were identified in 5 (29%) of the 17 children who had associated malformations.

Type of associated syndromes

The syndromes were Apert, Cleft lip/palate-ectodermal dysplasia, Kabuki, Oculo-Auriculo-Vertebral Spectrum, and Velocardiofacial (Table 1).

Discussion

This is the first documentation on the prevalence and type of syndromes in a cohort of Northeastern Thai children. The prevalence of associated syndromes in children with cleft lip and palate treated in KKU during October to December 2011 was 5 (4%) of the 123 patients, which was a little lower than the range of the 5-7% found in a previous report[7]. The difference could be explained by a different assortment of cases in the population based of the previous report[7] and the hospital based samples of the present study. The syndromes found in each patient, were: Apert, Cleft lip/palate-ectodermal dysplasia, Kabuki, Oculo-Auriculo-Vertebral Spectrum, and Velocardiofacial. Of the five syndromes, 4 (80%) have known genetic causes, including a single gene disorder in three patients and a chromosome abnormality in one patient with 22q11.2 deletion.

Apert syndrome is an autosomal dominant disorder that is caused by the mutation of fibroblast growth factor receptor 2 (*FGFR2*). S252W or P253R mutation of *FGFR2* causes retarded development of the skeleton and skull malformation resulting from premature fusion of the craniofacial sutures[11]. The patient has early fusion of coronal suture of the skull, maxillary hypoplasia, proptosis, bilateral syndactyly of hands and feet and developmental delay[11].

A male patient with cleft lip had ectodermal dysplasia, mental retardation, and syndactyly and was classified to have cleft lip/palate-ectodermal dysplasia (CLPED) syndrome[12,13]. CLPED is characterized by sparse and twisted hair, dry skin, palmoplantar keratoderma, delayed tooth eruption, cleft lip/palate, syndactyly of fingers/toes) and intellectual disability. CLPED is caused by mutations in the gene *PVRL1* (11q23-q24) which encodes nectin-1. It has been proposed that nectin-1 is a cell-cell adhesion molecule that is preferentially expressed in keratinocytes. Mutation in *PVRL1* may abolish nectin-dependent cell-cell adhesion[12-14].

Kabuki syndrome was suspected in a female patient who had elongated palpebral fissures with eversion of the lateral third of the lower eyelid, bilateral

Table 1. Type of syndromes and their relation to the type of clefts children were diagnosed with whom received continuous multidisciplinary treatment and follow-up care at the Tawanchai Cleft Center in Northeastern Thailand, 2011

Patient number	Syndromes	Cause*	Clinical features of the children	Sex	Type of clefts
1.	Apert	*FGFR2* mutation	Craniosynostosis, proptosis, bilateral syndactyly of hands and feet, developmental delay	Girl	CLP
2.	Cleft lip/palate-ectodermal dysplasia	*PVRL1*	Syndactyly, ectodermal dysplasia	Boy	CL
3.	Kabuki	*KMT2D* and *KDM6A* mutation	Elongated palpebral fissures with eversion of the lateral third of the lower eyelid, bilateral ptosis, prominent ears, hypotonia, developmental delay	Girl	CLP
4.	Oculo-Auriculo-Vertebral Spectrum	Unknown	Dysplastic left ear, hypoplastic left mandible	Boy	CLP
5.	Velocardiofacial	22q11.2 microdeletion	Tetralogy of Fallot, recurrent otitis media	Boy	CLP

CLP = cleft lip and palate; CL = cleft lip
* The cause has been searched in the http://www.ncbi.nlm.nih.gov/OMIM

ptosis, prominent ears, hypotonia, and delayed development. Kabuki syndrome is caused by mutations or deletions of lysine (K)-specific methyltransferase 2D (*KMT2D*) and lysine-specific methylase 6A (*KDM6A*). Kabuki syndrome is characterized by typical facial features including long palpebral fissures, eversion of the lateral one-third of lower eyelids, short columella with depressed nasal tip, large ears and tented upper lip. The patient usually experiences persistence of fetal fingertip pads, short stature and mild to moderate intellectual disability. Congenital heart defects, genito-urinary anomalies and cleft lip and/or palate occasionally occur [15].

A patient with oculo-auriculo-vertebral spectrum (Goldenhar syndrome) displayed, left hemifacial microsomia, dysplastic left ear, and hypoplastic left mandible. The common clinical presentation of this syndrome includes facial asymmetry, hypoplasia of facial musculature, microtia and hemivertebrae. Occasional findings are: epibulbar dermoid, cleft lip and palate, congenital heart and genito-urinary abnormalities. The etiology of this syndrome is unknown but may have a genetic cause in some cases[16].

A male patient with dysmorphic face, recurrent otitis media and Tetralogy of Fallot was diagnosed as velocardiofacial syndrome (VCFS). FISH testing of chromosome 22q11.2 by TUPLE1 probe revealed deletion. Clinical features of VCFS include facial dysmorphism, Pierre-Robin sequence, velopharyngeal insufficiency, congenital heart defects (particularly conotruncal heart anomalies), hypocalcemia from hypoparathyroidism and defect in the immune system, particularly cell-mediated immune response from aplasia or hypoplasia of thymus. Tetralogy of Fallot is the most commonly occurring heart defect in this syndrome[17]. However, we did not find hypocalcemia or immune defects in this child.

Study limitation

The present study is hospital based and the prevalence rate reported cannot be generalized for the whole Thai population. However, the present study was conducted in CLP patients attending the Tawanchai cleft Center, Faculty of Medicine, Khon Kaen University who were treated and received follow-up care until 4-5 years of age. Clinical information on each CLP child was reviewed by a pediatrician and a geneticist to ensure the accurate definition and classification. Some CLP children with lethal syndromes died before period of data collection (4-5 years of age); therefore, the prevalence of associated syndromes in patients with cleft lip and palate may be underestimated. Although some non-lethal syndromes may have been initially missed, the long follow-up period of 4-5 years with geneticist consultations can absolve the missing

cases. Therefore, the authors have confidence that the results of this study have certain value for clinicians and health care providers.

Conclusion

The prevalence of associated syndromes in patients with clefts of lip and palate treated in KKU from October to December 2011 was 4%. Recognition of the associated syndrome with the CLP is essential to assess the problems and risks faced by the patient. Proper knowledge and details of syndromes associated with CLP will help to provide necessary treatment and improve survival rates of these patients. Proper dysmorphology assessment and genetic study may lead to the appropriate methodology for prevention.

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Potential conflicts of interest

None.

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ความชุกและชนิดของกลุ่มอาการที่พบร่วมในการรักษาผู้ป่วยปากแหว่งเพดานโหว่ในช่วงอายุ 4-5 ปีของศูนย์ตะวันฉาย

กุณฑล วิชาจารย์, อวยพร ปะนะมณฑา, สุธีรา ประดับวงษ์, มนัส ปะนะมณฑา, วิบูลย์ วีระอาชากุล, บวรศิลป์ เชาวน์ชื่น

ภูมิหลัง: ความเข้าใจในสาเหตุทางพันธุกรรมของภาวะปากแหว่งเพดานโหว่ มีความสำคัญในการป้องกัน ดูแลรักษาและการพยากรณ์โรคของผู้ป่วย
วัตถุประสงค์: เพื่อศึกษาความชุกและชนิดของกลุ่มอาการที่พบร่วมในผู้ป่วยปากแหว่งเพดานโหว่ที่ภาคตะวันออกเฉียงเหนือ
วัสดุและวิธีการ: การศึกษาแบบย้อนหลัง ผู้ป่วยปากแหว่งเพดานโหว่อายุระหว่าง 4-5 ปี จำนวน 123 ราย ที่รับการรักษาที่ศูนย์ตะวันฉาย มหาวิทยาลัยขอนแก่นระหว่าง เดือนตุลาคม ถึง เดือนธันวาคม พ.ศ. 2554 ข้อมูลได้จากการทบทวนเวชระเบียน
ผลการศึกษา: ผู้ป่วยปากแหว่งเพดานโหว่จำนวน 123 ราย พบสภาพวิรูปอื่นร่วม 17 ราย (ร้อยละ 14) และ พบเป็นกลุ่มอาการ 5 ราย (ร้อยละ 4) ผู้ป่วยที่เป็นกลุ่มอาการ 5 ราย คิดเป็นร้อยละ 29 ของผู้ป่วย 17 รายที่มีสภาพวิรูปร่วม กลุ่มอาการที่พบได้แก่ Apert, Cleft lip/palate-ectodermal dysplasia, Kabuki, Oculo-Auriculo-Vertebral Spectrum และ Velocardiofacial
สรุป: ความรู้เกี่ยวกับกลุ่มอาการที่พบร่วมกับปากแหว่งเพดานโหว่จะช่วยในการดูแลรักษาผู้ป่วยตลอดจนนำไปสู่การป้องกันโรค