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Oro-facial clefting and associated risk factors in selected families in General Santos City, Philippines

Florence Lasalita-Zapico*[1], Adrian Peñaflorida[1], Catherine Hazel Aguilar[1], Lyn Jean Laniton[1], Eillen Gay Palarpalar[2]

1 Science Department, Mindanao State University-General Santos City, The Philippines 9500
2 General Santos City District Hospital, General Santos City, The Philippines 9500

E-mail : florence.zapico@gmail.com Contact No : +63-083-3018349

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Abstract

This paper presents family histories of ten families with newborn babies having non-syndromic cleft lip with/without cleft palate (CL/P). Through guided interviews, information about recurrence of CL/P within the families and potential risk factors were elicited. Pedigrees going back three generations were then constructed based on obtained data. Results of the study underscored the complex nature of CL/P expression with contributions from genetic and environmental factors. Conversations with families revealed potential risk factors such as advanced parental ages, indiscriminate use of antibiotics and over the counter drugs such as naproxen, paracetamol, ibuprofen and mefenamic acid for common ailments. X-ray irradiation, exposure to secondary smoke and chemicals in the workplace were also some of the identified risk factors. While results are inconclusive because of the small number of families interviewed, the study nonetheless presented baseline information of CL/P incidence in GSC where none is available. A larger sample size will result in better identification of risk factors and will help in the elucidation of the aetiology of CL/P in General Santos City.

Key words : cleft lip, risk factors, pedigrees, General Santos City

INTRODUCTION

Isolated, non-syndromic cleft lip with or without cleft palate (CL/P) is a common oro-facial disorder that occurs in 70% of all reported oro-facial cleft cases[1]. Its high rate of recurrence within families and its sporadic nature of expression indicate that an active interplay of genetic and environmental factors controls this trait[2]. While CL/P does not usually result to mortality, it has high morbidity among affected individuals. Moreover, the interventions needed to improve the quality of life of a CL/P patient are usually costly and put added financial burden to the family.

Many studies have revealed regional and racial differences in CL/P prevalence with Asians having highest risk for this disorder. Moreover, [3] discovered that among all Asians, Filipinos are more at risk than Pacific Islanders. A non-governmental organization in the Philippines (Operation Smile) with a specific thrust of improving the quality of life of CL/P sufferers, partitions 20-50% genetic contribution to CL/P expression with the remainder being ascribed to environmental or G x E interaction effects. Yet there are contrasting claims about the nature of CL/P inheritance (polygenic *vs* oligogenic; dominant *vs* codominant; multifactorial or governed by a major locus etc.) which can be read in various literatures. This long and oftentimes acrimonious debate about semantics notwithstanding, experts from different disciplines are coming together utilizing myriad techniques and technologies with the unified aim of elucidating the mechanism of CL/P transmission. This present study was therefore undertaken to examine the pattern of inheritance of CL/P in selected families in General Santos City (GSC) and determine associated risk factors for this oro-facial disorder. Pedigree analysis was used because it is a useful genetic tool which can provide clues as to the pattern of inheritance of an anomaly in a manner that is cost-effective and that abides by ethical and moral standards. Furthermore, demographic data and personal interviews can also shed light on certain environmental influences that might have intensified the risk for CL/P [1].

MATERIALS AND METHODS

Figure 1. Map of General Santos City

General Santos City, a medium-sized city located in the southernmost tip of the Philippines, faces Celebes Sea and is considered as the southern backdoor of the country due to its proximity to Brunei, Indonesia and Malaysia (Figure 1). This city, which is a strategic entry point for the East Asian growth area, is on the verge of economic take off as proven by economic development it has experienced during the past few years. This present study focused on General Santos City families with at least one newborn infant having isolated, non-syndromic CL/P. Other inclusion criterion was delivery in major medical facilities (MFs) in GSC during 2009 to 2012. CL/P infants delivered at home were not considered for this research.

This research is qualitative and descriptive in nature. The research respondents were selected from in-patient hospital records of MFs and letters of informed consent were sent to prospective families with newborn infants having CL/P. The

prospective respondents were then located through details in their hospital records and their participation to the study was solicited. Consenting families were interviewed using a validated and pre-tested questionnaire modified from [4] and [5]. Other cases of CL/P in the families as well as some potential risk factors were noted in the interviews. From the interviews, cases of isolated CL/P were traced across 3 generations and family trees (or pedigrees) were constructed using standard symbols.

RESULTS

Retrospective inspection of hospital records showed CL/P prevalence rates of 1.84 (2009), 3.30 (2010), 14.57 (2011) and 6.94 (2012) for every 10,000 births in GSC. Most of the cases of CL/P in GSC were bilateral and unilateral types. Hereunder are 10 families having cases of CL/P and their corresponding pedigrees:

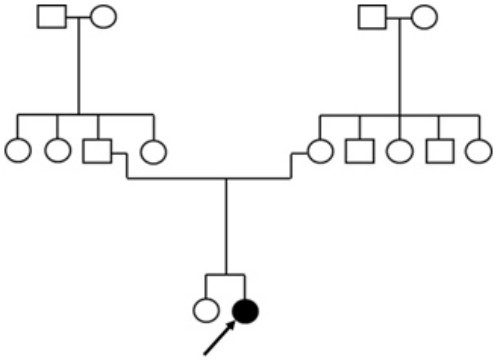

Fig 2. Family #1 Pedigree

*Shaded figures with arrows indicate affected individuals (proband)

The first couple had 2 daughters, one of which had CL/P (Figure 2). The father, aged 42 was a fireman and the wife (a businesswoman) was 39 when she had the affected child. No major medical episodes were mentioned by the family except for the father's slight hypertension which was kept under control by medication. The family also did not have any known record of CL/P and the mother could not recall of exposure to any potential risk factors or teratogens.

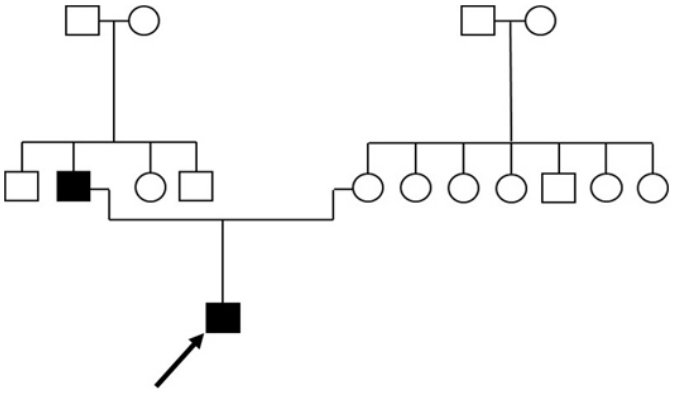

Fig 3. Family #2 Pedigree

The proband (a boy) was born to an affected father and a normal mother (Figure 3). Both in their 20s, the father (a driver by profession) and his wife had one son who had bilateral CL/P. No consanguinity was reported though the family disclosed that the paternal grandparents were normal in terms of their oro-facial aspects. The variable expression of this oro-facial anomaly was demonstrated by the infant who had CL/P and his father who had cleft lip only.

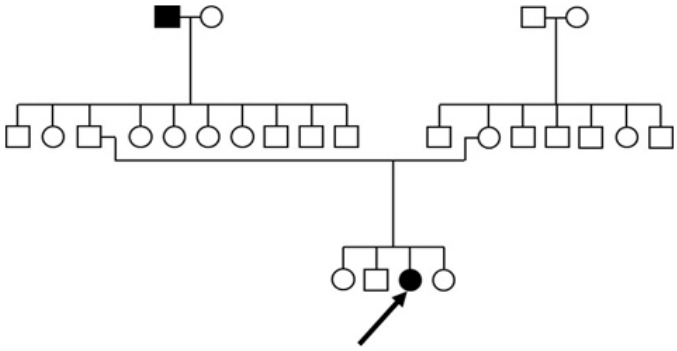

Fig 4. Family #3 Pedigree

Family 3 consisted of 4 children with the third child (a girl) manifesting CL/P (Figure 4). The female proband was born to phenotypically normal parents who were in their 30s. Interviews with the family revealed that a grandfather on the paternal side also manifested the condition. The affected infant had a bilateral CL/P while her grandfather had an unspecified oro-facial cleft. Conversation with the mother revealed that while pregnant, she engaged in a home-based leather/shoe manufacturing business for supplemental income. She also reported of having radiation exposure (X-ray) during the 5th month of pregnancy.

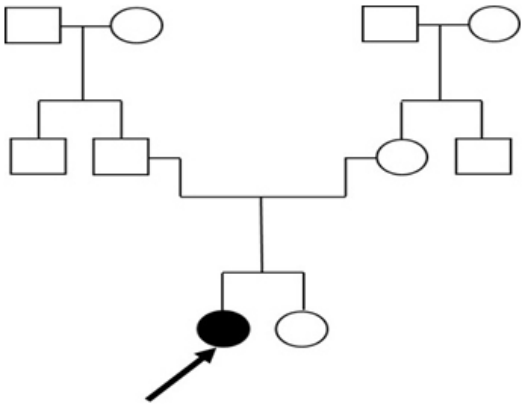

Fig 5. Family #4 Pedigree

Family # 4 had two daughters, one of whom had CL/P (Figure 5). This affected child was born to normal parents who were in their early 20s. Interviews with the family revealed very liberal use of various drugs by the mother for common ailments without consultations with her obstetrician. While pregnant, the mother took amoxicillin, mefenamic acid, Medicol (ibuprofen) and Alaxan (paracetamol + ibuprofen). Furthermore, casual talks with the family also revealed a 3rd degree uncle on the father's side and a 2nd degree uncle on the maternal side having CL/P.

Pedigree # 5 further provides additional evidence for the multi-factorial nature of CL/P expression (Figure 6). The affected son was born to a 28-year old mother who while pregnant inhaled cigarette smoke of her husband on a permanent basis.The male proband had bilateral CL/P in which the cleft lip was surgically repaired (Fig. 12). While pregnant, the mother also used ferrous sulfate and herbal supplements indiscriminately. No history of

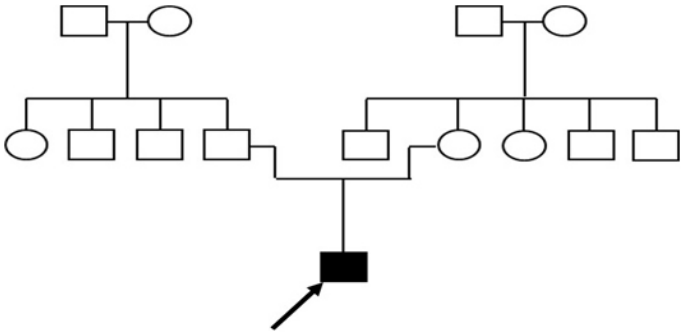

Fig 6. Family #5 Pedigree

CL/P was recorded on the maternal side although the father, a 34-year old driver, revealed that he had a first cousin who had CL/P.

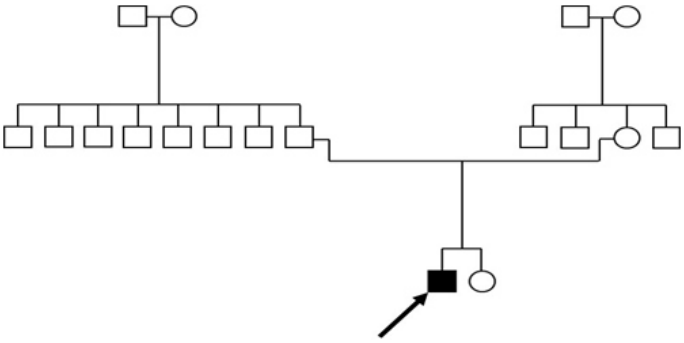

Fig 7. Family #6 Pedigree

For pedigree # 6, the proband was a young male infant who was born to a 21-year old mother and a 28-year old father who was a heavy smoker (Figure 7). The mother also took Flanax Forte (naproxen) for pain and inflammation while pregnant. There was no report of consanguinity and the family's medical history was relatively uneventful except for very minor infectious diseases like colds and flu.

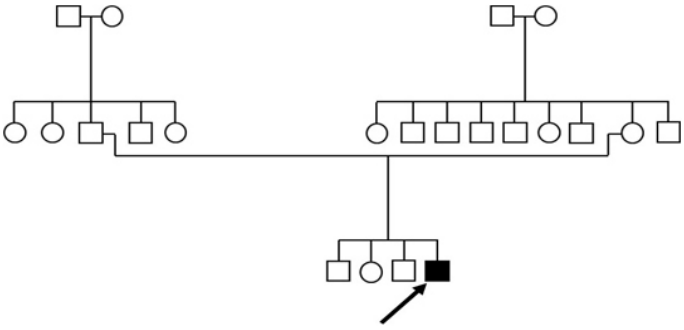

Fig 8. Family #7 Pedigree

An affected son in a brood of four (Figure 8) was born to parents in their 40s. Tracing the family lineage up to 3 generations back showed no other person manifesting the condition. While pregnant, the mother took various food supplements like evening primrose oil and Omega fish oil. Aside from mild anemia on the case of the mother, no other disorders of medical significance were noted in the family.

The case of the affected daughter in this pedigree seems like a fluke since nobody else in the family (up to the grandparents) showed the condition (Figure 9). The daughter with CL/P was

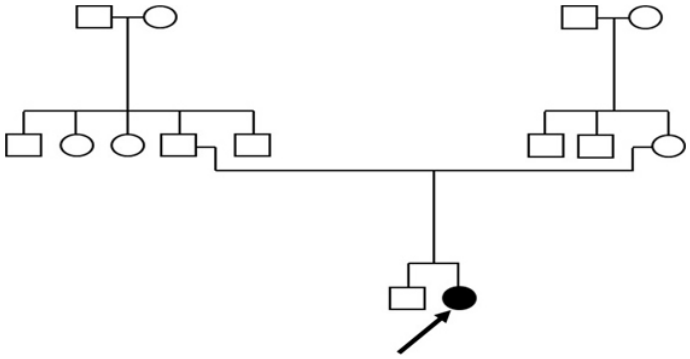

Fig 9. Family #8 Pedigree

born to a 29- year old salesman and a 31-year old housewife. There was no record of major medical illness or of consanguinity in their marital union. Not known to smoke or to drink while pregnant, only the mother's intake of ibuprofen for body pains seemed suspicious.

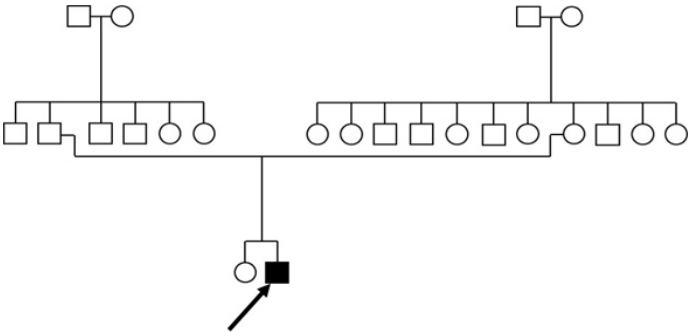

Fig 10. Family #9 Pedigree

Figure 10 shows a male proband born to parents in their 20s. The mother, a housewife, suffered from diabetes, had post term pregnancy and delivered her baby way past the 42nd week. Except for exposure to her husband's cigarette smoke while pregnant, the woman was not exposed to known risk factors for CL/P. No consanguinity or major medical illnesses were recorded during the interviews. It is also relevant to note that a first cousin on the father's side was also affected with the condition, indicating a strong genetic component.

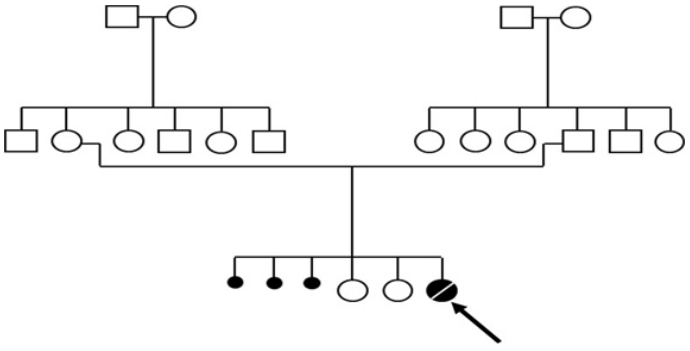

Fig 11. Family #10 Pedigree

* indicates still births

For pedigree # 10, the couple in their early 40s had 3 stillborn babies, 2 normal children and another with CL/P (Figure 11). The mother had urinary tract infection (UTI) during pregnancy and was prescribed cephalexin by her obstetrician. Examination of

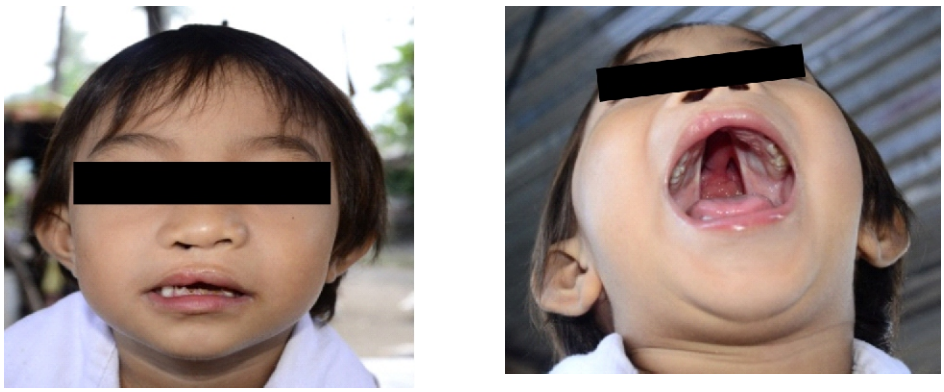

Figure 12a&b. : Male proband (Pedigree #5) showing surgically repaired cleft lip and unrepaired cleft palate

family history revealed no consanguinity or significant medical conditions except for a mild case of hypertension for both parents which they managed through maintenance medicine.

DISCUSSION

The complex interactions that underlie CL/P inheritance have confounded scientists and medical practitioners up to this date. Moreover, its variable phenotypic expression (degree/nature of clefting etc) and some memory lapses about CL/P cases among relatives interviewed result in underreporting of the condition. For this particular study, findings indicate a very active genetic component especially for pedigrees # 2, 3, 4, 5 and 9. Pedigree# 2 specifically, suggests that CL/P is inherited in an autosomal dominant fashion with variable expressivity. Results of the study are reminiscent of those by [6-11]. On the other hand, pedigree # 3 demonstrates the sporadic nature of expression of CL/P and while CL/P cases tend to aggregate within the family, a straight forward Mendelian pattern of inheritance is rarely seen [12].

Results also provide evidence, albeit tentatively, of an interplay of genetic and environmental (GxE) factors in CL/P expression.For pedigrees 1 and 7, a likely risk factor is child bearing during the later years of life. That older parents are at greater risk of having children with CL/P had been reported by[13-16]. Furthermore, two cases of CL/P (Pedigrees # 5 and 6) can be ascribed to cigarette smoke exposure by pregnant mothers. These findings about cigarette smoking as a CL/P risk factor had been put forward by numerous authors [17-27]. For Pedigree # 3, another possible risk factor was occupational exposure of the pregnant mother to solvents used in leather/shoe making.[28]and[29] reported about purported teratogenic effects of these solvents during pregnancy.

Medicines and nutritional supplements taken by pregnant mothers are also considered as potential risk factors for CL/P incidence in selected families. The mother in pedigree # 5 took Pregnamil (herbal supplement) during the early months of pregnancy. Presently, teratogenic effects of herbal supplements are not well studied and cases of congenital malformations are mostly anecdotal[30]. Moreover, cases of CL/P in pedigrees # 6 and 8 can possibly be attributed to unregulated use of ibuprofen, mefenamic acid and amoxicillin. Several studies report that over the counter drugs like ibuprofen [31], mefenamic acid [32]and amoxicillin[33] when taken during the early trimesters of pregnancy increase the risk of CL/P. In addition, naproxen, a non-steroidal anti-inflammatory drug, is the suspected cause of CL/P in pedigree # 6. The teratogenic effects of naproxen and other non-steroidal anti-inflammatory drugs (NSAIDS) had been widely published in scientific literature [31][27].

The last pedigree (#10) clearly demonstrates the ravages of advanced parental ages, possibly cephalexin intake and exposure to passive smoking on embryonic development. An antibacterial agent such as cephalexin can be potentially teratogenic at higher doses, yet the magnitude of its effects on embryonic development is still subject to a lot of controversy [34-35]. Furthermore, inquiries made about the causal nature of the 3 stillbirths in this family revealed an unknown cause. In Brazil, [36] disclosed that of all risk factors evaluated, only a history of stillbirths was significantly correlated with oro-facial cleft incidence.

CONCLUSION

Since reports about CL/P cases are fragmentary with certain findings applicable to certain populations, conflicting reports are oftentimes encountered if one does literature review. In this study, GxE interactions in CL/P cases are positively underscored. Among the risk factors identified were increasing parental ages and passive smoking. Over the counter drugs for pain (ibuprofen, naproxen and mefenamic acid) and antibiotics such as amoxicillin and cephalexin were taken by some mothers while pregnant. While amoxicillin has been firmly established as teratogenic, there are conflicting theories about cephalexin and its purported ill effects on embryonic development. What makes it worse for the baby is that these drugs cross the placenta and become extruded with breast milk [37]. Efforts should therefore be made to educate pregnant women about the perils of indiscriminate drug use. With this baseline data from the study, the Philippine government will have bases for interventions targeting pregnant women and newborn babies. Through these interventions, families coming from the lower economic strata of society can avail of social services that they urgently need.

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