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Non-syndromic cleft lip and palate: Could stress be a causal factor?

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Abstract The aetiology of non-syndromic cleft lip and palate has as yet not been clearly defined. Familial relationships, environmental toxins and nutritional status have all been considered without conclusive results, although in some studies a potential link between non-syndromic cleft lip and palate and any one or more of these factors has been proposed.

Elevated stress, particularly an extended term of traumatic stress, can lead to oxidative damage at the cellular level via hypothalmus–pituitary–adrenal (HPA) axis dysregulation, high cortisol and cytokine production. The effect of this hormonal shift is to re-direct the blood supply to the mother's muscles, thereby reducing the supply to the placenta, causing a potential nutritional deficiency which may then result in a genetic alteration in the foetus.

Mothers with a child aged two years or younger who had been born with a cleft, who were members of CleftPals, a family support group, volunteered to be participants in this qualitative study. The research first called for a survey to be completed by the mother and this was then followed by an interview conducted by the researcher. The study involved families living in the three eastern States of Australia.

The results suggest that physical and/or emotional stress may well be implicated in clefting. While little work has been done in considering stress as a causal factor, the existing literature suggests, as does this study, that elevated stress levels at, or soon after, conception appear to affect foetal development.

Introduction

Three forms of oral defects have been considered in this study: cleft lip (CL), cleft palate (CP) and cleft lip and palate (CLP). Throughout this paper the letters 'U' will be used for unilateral and 'B' for bilateral and the abbreviation CLP will be used as a generic term unless stated otherwise.

The aetiology of non-syndromic CLP, a state where either the lip or palate or both have not completely formed, has to date not been adequately determined. Most researchers suggest that the cause is multifactorial.

Non-syndromic clefting is distinct from syndromic clefting in that the clefts to the lip and/or palate are the only anomalies, while in syndromic clefting the cleft occurs with

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other well-documented abnormalities, such as respiratory or cardiac anomalies. Syndromes that are associated with clefting include Van der Woude, Teacher-Collins and Pierre Robin as well as several others. In these cases the clefting is generally the lesser of the concerns.

The author has been a Director of a charity called Operation Rainbow Australia Limited for nearly 20 years. This organization sends medical teams to third world countries to provide surgical support to children with facial anomalies who are living in poverty. The question to the surgeons has always been: 'why not find the cause rather than repair the result?' The answer has always been: 'surgeons do what surgeons do best — operate'.

As this was not an acceptable answer a research program was established. This paper covers one segment of a much larger study into the aetiology of CLP, the question being 'what causes this birth anomaly?'

At an early stage in this investigation stress immediately before or at an early stage in the pregnancy appeared to be involved as a risk factor which may be related to these anomalies.

Literature review

CLP has been recognized for many centuries. The earliest known reported reference to clefting comes from China[1] where it is claimed that in AD 390 an unknown surgeon successfully closed a cleft on an 18 year old girl, 'Wei Yang-Chi', who later became the Governor General of several provinces.

More rigorous research into CLP appears to have started early in the 20th century.[2] No clear linkages have been established that point to definitive causative factors. Most researchers suggest that the cause is multifactorial, and indeed this may well be the case. Research papers covering genetics, familial associations, nutrition, drug use by the mother and environmental toxins have been canvassed to determine whether there could be any connection which may lead to a better understanding of the nature of this problem.

Incidence

CLP, CL or CP is not something that has just appeared in our society, nor is it confined to an individual group within a nation or socioeconomic sector. The birth prevalence of CLP was reported to be 1 per 1000 among Caucasian populations in England.[3] In Asian populations, the reported prevalence ranges from 1.11 to as high as 2.06 per 1000.[4–7]

In Australia the records are kept on a State by State basis, with the quality of the recording varying greatly. No differentiation is made between syndromic and non-syndromic forms of clefting. Using Queensland and Victorian data, the incidence is 1.5 and 1.8 per 1000, respectively. These statistics[8] relate to 697,513 births in Queensland and 795,323 in Victoria over a five-year period.

The researcher visited the Philippines at the start of this research project as part of a surgical mission, as the incidence of clefting in that country was reportedly much higher than in other countries. The researcher found that the frequency of CLP at a national level has as yet not been determined as the Government does not keep a record of such birth defects. One study in that country[9] analysed the hospital records of 47,969 newborns over six sites between 1989 and 1996 and found that the incidence was 1.94 per 1000 for all clefting, with the higher incidence of 2.3 per 1000 for a second child also having a cleft.

In the Philippines a total of 1,640,698 births were recorded in 2002. Sixty seven percent of these births occurred in the home and only 28% of the children were born in hospitals. The Philippine Health statistics do not indicate where the remaining 5% were born but presumably the person completing the birth record omitted to fill in that section indicating place of birth. Of the total births only 67% were attended by medical professionals and some of these professionals may have been merely health workers. This means that the research carried out by Murray et al.[9] was skewed towards those of a higher socioeconomic level who could afford to have their children born in a hospital.

Doctors working in the Philippine Hospital (Quezon City) indicated that it was their opinion that clefting was a problem of the poor, suggesting that the incidence of CLP among the general population was much higher than that recorded by the hospitals. The link between low socioeconomic status and stress has been well documented.[10,11] The authors indicate that this group has a higher allostatic load due to less coping skills, poorer lifestyle choices and in most cases less freedom to choose their desired outcomes. The poor in the Philippines in general are housed in shanty type accommodation and exist on not much more than two handfuls of rice per day. This then does not constitute a balanced diet which, when combined with the environment that they are exposed to on a daily basis clearly leaves them open to disease and other medical problems.

Stress

Initially this research project aimed to consider other possible causal factors of CLP, such as: the mother's alcohol and drug use, smoking habits and nutritional supplementation taken prior to and during the pregnancy. However, even at an early stage in the study stress seemed to be an issue and this led to considering other work that had been done linking stress to clefting.

Stress levels affect the metabolism and thus the environment in which the cells reproduce and develop. If stress levels are low or of short duration, physiology and cell development and replication can return to normal, while continuously high stress levels lead to possible abnormal development or cell necrosis.[12] The development and function of foetal tissue and organs is directly proportional to the amount of blood they receive. When passing through the placenta, the hormones of a mother experiencing stress will profoundly alter the distribution of blood flow in her foetus and change the character of her developing child's physiology.[13,14]

A study in Czechoslovakia[15] retrospectively analysed the stress levels of mothers who gave birth to children with clefts. They separated the children into two groups: (1) children with bilateral cleft lip and palate (B/CLP), and (2) children with all other types of clefts. The finding which they describe as "the most impressive"[15] part of their study showed that in group 1, 47.1% of mothers "were severely disturbed with depressive and anxiety states. Family conflicts, alcoholism of the father,

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death or disease of close relatives were common findings."[15] In group 2 the figure was 35.7%.

A recent study carried out by researchers in Basrah, Iraq[16] shows that the incidence of clefting in the period 2003–2005 had doubled compared to 1996–1998. The study cites increased stress levels, poor access to adequate nutrition and an increase in environmental toxins as possible causal factors.

These two studies[15,16] suggest that there may be an association between stress of the mother during pregnancy and occurrence of CLP. The authors suggest that if a cleft occurs it would seem evident that a genetic alteration must have taken place. The increase in incidence of clefting in the Iraqi population within a short period of time suggests that there are external forces at work leading to the genetic alteration. In the Basrah study it was suggested that these external forces could be stress due to the war, nutritional deficiencies or environmental toxins.

Methodology

Families who had a child two years or younger with a cleft were included in the study. Cases that were clearly syndromic in nature were excluded. All families were associated with the family support group called 'Cleft Pals' through which contact was made with the mother. Cleft Pals, which operates in all states of Australia, agreed to indicate to their members that research was to be carried out and asked for volunteers to participate.

Only families living in those States of Australia (Queensland, New South Wales and Victoria) with the highest population were included to reduce the travel costs should it be necessary for face-to-face interviews. This also ensured that the families lived in different environmental conditions. Considering that environmental toxins could be involved in clefting, as some researchers have suggested,[17–19] it was essential to ensure that families included in the study came from different geographic locations so that any localized toxin exposure did not skew the results.

The study, carried out in the years 2007–2008, was questionnaire-based and covered areas that may affect the health of the developing foetus. A number of physical and lifestyle questions, such as whether the parents smoked, the mother consumed alcohol during pregnancy, whether she had taken any medication or nutritional supplements, and details of her age at conception, height and weight were included in the questionnaire. She was also asked for the medical history of both parents, whether either had had a cleft at birth, and whether there was any history of clefting in the family. The mother was not asked whether conception had been via IVF but where it is recorded the mother had considered this to be a stressful process. After completion of the questionnaire the parents (often just the mothers) were contacted by the researcher to verify the data that had been submitted.

Only demographic data and the responses to questions relating to the mother's stress levels and/or events that occurred around the time of conception were considered for inclusion in this research paper. As stress levels vary, as do the coping skills of those experiencing this stress, it was thought that the type and degree of clefting may be directly proportional to the level of perceived stress. In order to determine if this was the case the responses were classified into three groups according to the level of perceived stress.

The Questionnaire

The part of the questionnaire relating to mental/emotional stress that the mother experienced at or around the time of conception contained the following questions:

Question 1.

How would you describe yourself?

- Easy going
- Worries sometimes
- Worries often
- Continually worries about the future

Question 2.

In the period one month prior to conception to two months after conception, was there any event that occurred in your life or your family that caused you anxiety or stress above the normal stresses of life?

☐ Yes ☐ No

If yes please describe:

Each questionnaire received was followed up by communication with the mother either face-to-face or by phone to clarify the data submitted.

Ethics

The research project was approved by the Human Research Ethics Committee at Southern Cross University (HREC # ECN-05-163). The authors did not approach any of the participants directly to seek their inclusion. The study was outlined to the family support group CleftPals who circulated the information to their members. Those wishing to participate who fell within the study parameters then contacted the researchers after receiving an information package.

Results

Forty-seven families responded, representing 48 children. Two children were included from one family: the first born with a U/CL and the second with a CLP. One family had twins, one being born with a U/CL and the other with no anomaly.

Four of the children had syndromic clefts and so those families were excluded. This left 43 families and 44 children in the study.

The results are summarized in Tables 1 and 2.

Mother's age at conception of the child

The mean age of the mothers at conception giving birth to a child with CLP was 31.7 (SD = 5.83) years. The ages ranged from 21 to 44 years.

Position of child in family

Forty-nine percent of the CLP children were first born, and 51% were the second child to be born in the family. None of the mothers had more than two children.

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Table 1 Stress analysis.

Degree of stress	Stress type	Stressors
Group 1: Traumatic stress	Employment	Redundancy, bullying, resigning due to stress, partner redundancy
	Family	Family arguments, leaving family, family separation, death in family, entered into marriage, relationship breakdown, left husband, husband did not want child, husband's use of alcohol
	Pregnancy	IVF, twins diagnosed, sex of baby not wanted, difficulty to conceive
	Psychological	Suffering depression, obsessive compulsive disorder
Group 2: Elevated stress	Relocation	Leaving husband, town, or country
	Employment	Relationship with employer, work overload
	Family	Stressed from first child, fatigue, death in family
	Pregnancy	Difficulty conceiving
	Psychological	Continual worry, concern about health of foetus
	Relocation	Moved house
	Physical	Major haemorrhage, illness

Sex of child with cleft
Eighty one percent of the children with clefts were male.

Types of clefts
Twenty-one percent of children had a unilateral CL only and 18.5% had a CP as the only anomaly. Seven percent had a B/CLP and 53.5% had a U/CLP.

Ultrasound testing did not detect any of the single CP anomalies, and it did not detect four of the CLP abnormalities, two of these being B/CLPs. However, it did detect all other anomalies no later than 20 weeks into the pregnancy.

BMI and weight of mother at conception
The average body mass index (BMI) of the mother ranged from 18.4 to 34.3, with a mean of 24.1 (SD = 3.47). The mother's weight at conception ranged from 47.0 kg to 104.0 kg with a mean of 67.0 kg (SD = 12.15).

Length of pregnancy
Sixty percent of mothers carried the child to full term and 4.6% beyond full term by 10 days to 3 weeks. The mothers who did not carry to full term gave birth between 34 and 39 weeks (35.4%).

Birth weight
The mean birth weight was 3.37 kg (SD = 0.65) with a range of 1.2 kg to 4.94 kg.

Mental/emotional stress
In 16 of the 43 families (37.2%) the mothers indicated that at or around the time of conception their lives were highly stressful. In a further 15 cases (34.9%) the mothers indicated stress or anxiety but of a much milder nature. There was no possible way of quantifying the level of stress as experience of stress is very subjective. However, some level of stress or

Table 2 Summary of results.

Demographics	Group 1: Traumatic stress	Group 2: Elevated stress	Group 3: No stress
	Mean ± SD	Mean ± SD	Mean ± SD
Mother's age at birth	33.8 ± 5.46	32.2 ± 5.70	30.4 ± 6.32
Mother's weight at conception	70.9 ± 14.98	64.9 ± 8.80	67.5 ± 11.61
BMI	25.8 ± 3.49	23.1 ± 3.10	24.5 ± 3.47
Child's birth weight	3.6 ± 0.38	3.3 ± 0.69	3.5 ± 0.84
Sex of child			
Male	14	12	10
Female	2	3	3
Position of child in family			
First child	7	9	6
Second child	9	6	7
IVF conceptions	1	3	0
Cleft type			
U/CL	3	2	3
CP	5	1	2
U/CLP	6	11	8
B/CLP	2	1	0
Total clefts	16	15	13

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anxiety was evident at or around the conception period in 72% of cases (n = 31).

Individual responses

Obviously the researchers were not able to determine quantitatively the level of stress or the coping skill of the participant but relied purely on the mother's perception regarding degree of trauma and therefore stress. Obviously what is traumatic to one individual may in fact be a minor irritation to another. The category and types of stressors, as indicated by the mothers' responses to question 2 in the questionnaire, were thematically analysed and are listed in Table 1.

The following responses by the mothers to open-ended questions are examples of the issues that were highlighted by respondents.

Traumatic stress: 'Extremely stressful job involving bullying, finally leaving job. Also at the time tension and arguing with the family. I removed myself from the family and now do not visit or phone'.

Elevated stress: 'Completely fatigued with second child. Prone to worry and get stressed. Very tired and exhausted'.

Grouped results

While stress, as defined by the women themselves, seemed to be the major risk factor involved in this study the results were further grouped to determine whether any of the other items, e.g. BMI, might also be linked to CLP. The results were first separated by stress level and then the various demographics listed for each group.

The decision regarding where to group each mother was based on the mother's own definition of the level of stress that occurred.

Group 1 included cases where a specific traumatic event had occurred.

Group 2 included cases where elevated stress was noted.

Group 3 included cases where the mother indicated that there was no particular highly stressful incident and that she coped well with day-to-day stress.

The results of this grouping are set out in Table 2.

Discussion

The average birth age for Australian mothers was 27.3 years in 1985 and 30.7 years in 2005, an increase of 3.4 years.[8] The birth age of the study group of 31.7 years is slightly higher than the mean age group of mothers giving birth in 2005, and allowing for the trend upwards is probably much closer to the age group for 2008.

Considering that there was even distribution of clefts between the first and second born child it suggests that clefting is quite random and that external factors are much more likely to trigger a genetic response. However, what could have changed for the mothers between the first and second pregnancy are factors related to their lifestyle, marital situation, nutritional status and/or stress levels. If pregnancies were in close succession the mother may not have been able to recover fully from the nutrient drain to the first child. We did not ask whether there had been a partner change since the birth of the first child where the child with the cleft was the second born. Obviously this should be done in future research.

The results show that the majority of the children born with a cleft are male. Statistics published for Victoria support this.[20] No reason to date has been established to understand this phenomenon. It does suggest, however, that the genetic alteration(s) that result in CLP are associated with the X Chromosome. The proposition is that as a male has only one X chromosome; any interference in that area may be more damaging to the foetus than a similar shift in the female, where two X chromosomes are present. Recent research[21] has linked the X chromosome gene TBX22 with isolated CP. As there are a number of T-Box genes it is possible that either TBX22, or one closely related to it, could be involved in the other anomalies.

The absence of a direct link of the child with the cleft to past generations tends to suggest that clefting is not hereditary and probably therefore not a genetic trait. Even if there is a genetic trait, it would seem that for the gene to be expressed some external factor needs to trigger the genetic response, such as oxidative gene damage.[22]

As clefting has occurred by 12 weeks' gestation[23] it suggests that perhaps the first ultrasound should be undertaken between 12 and 20 weeks, as opposed to just one at 20 weeks. Should an ultrasound be taken at both 12 and say 18 weeks, doctors could be more confident about the absence of facial anomalies, with the exception of an isolated cleft palate.

In Australia it is quite normal for an expectant mother to have an ultrasound at 12 and 20 weeks. The question of safety in having ultrasonography has been considered[24] and the conclusion of the World Health Organization was that the use of this technique during pregnancy appears to be safe. The meta-analysis which was used to consider the safety of this procedure included 6716 citations and 19 from secondary sources. It also included 61 publications reporting data from 41 different studies: 16 controlled trials, 13 cohort and 12 case-control studies. The authors are therefore not opposed to the judicious use of this technique if it can potentially be helpful to the mother and the baby. Early detection of a cleft in a foetus allows the parents to seek information on the special needs this child will require when born.

The authors considered whether body weight may play a role in clefting. A normal range of BMI for women could be considered to be between 18.5 and 24.9.[25] The women in this study tended to be at the top end of this range, with the variation in weight in this study being quite wide. BMI alone could not be considered as having influenced the results. While obesity has been considered to be a risk factor by other researchers[26,27] these results do not support that hypothesis. Certainly within the sample group some women were overweight at conception but this cannot be taken as a generalization. The average BMI of the sample group also supports this fact. Therefore, other factors may have been implicated, although to be certain that insulin resistance is not involved serum insulin analyses would be required. Insulin resistance is the forerunner to type 2 diabetes which in turn is associated with obesity and is associated with an inflammatory state of the body.[28] Inflammation causes oxidative stress and has the potential to harm genes.[29]

The individual responses showed that the mothers in Group 1 experienced quite traumatic events around conception or in the first few weeks of the pregnancy. The level of stress is difficult to quantify as each individual copes in different ways. Indeed, even some of the events experienced by Group 2 could be traumatic in the eyes of the person and yet when viewed by

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others be considered as normal events in everyday life. We can only say that the women themselves considered these as stressful events.

The women in group 3 had children with clefts yet emotional stress did not seem to be a risk factor. Considering that stress for instance also derives from nutrient depletion or imbalance, toxins or inflammation this could still articulate into oxidative damage on a cellular level. As other researchers have stated, clefting could be multifactorial with other risk factors being prevalent, which to date, both others and we have not been able to isolate. Research is currently under way to explore this further.

Stress and pregnancy

Oxidative damage can result from nutritional deficiencies and/or the presence of environmental toxins.[22,29] However, physical and emotional stress, both of which result in altered cortisol levels, could also be involved. Such stressors in themselves can lead to oxidative damage at the cellular level via hypothalmus—pituitary—adrenal (HPA) axis dysregulation, high cortisol and cytokine production.[30] High cortisol levels have been linked to abdominal adiposity, insulin resistance and metabolic syndrome,[31] all of which may be involved in oxidative damage.

Stress levels affect the environment in which the cells reproduce and develop. If stress levels are low or of short duration, cell development may be impeded but can return to normal, while continuously elevated stress levels lead to possible abnormal development or cell necrosis.[12] The development of foetal tissue and organs is directly proportional to the amount of blood they receive, and hence their function. When passing through the placenta, the hormones of a mother experiencing stress may profoundly alter the distribution of blood flow in her foetus which could potentially lead to changes in the physiology of her developing child.[13,14]

Stress may be involved in a myriad of other disorders, and relaxation methods such as meditation are often recommended during treatment in order to minimize stress. In this study we recognize that stress opens up a large field of endeavour but we restricted our investigation to the role of emotional stress in the occurrence of CLP. Should the stress theory prove correct then future studies could be more widespread and look at the effect elevated stress has on other first trimester issues.

Conclusion

Of all of the criteria assessed, mental/emotional stress appears to be a likely risk factor in the occurrence of CLP. To date this has only been considered by a very small number of other researchers.

As stress is experienced subjectively and reactions to the same stressor are dependent on the coping skills and resources of the individual, there was no possible way to quantify the degree of stress other than assess it qualitatively. Certainly it does indicate that in any future studies attempts must be made to determine the level of stress, how this affects the biochemistry of the pregnant woman, and what effect that may have on the developing foetus. This could be assessed via stress questionnaires, and from both blood and urine testing during the pregnancy. Oxidative stress can be measured quantitatively using samples of either blood or urine. Further studies are currently under way.

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