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Foetal alcohol syndrome: a dental and skeletal age analysis of patients and controls

Sudeshni Naidoo*, Gustav Norval**, Sonja Swanevelder*** and Carl Lombard***
Departments of *Community Oral Health and **Diagnostics, University of the Western Cape, and
***Biostatistics Unit, Medical Research Council, Tygerberg, South Africa

SUMMARY Foetal alcohol syndrome (FAS) consists of multisystem abnormalities and is caused by the excessive intake of alcohol during pregnancy. The teratogenic effect of alcohol on the human foetus has now been established beyond reasonable doubt and FAS is one of the most important human teratogenic conditions known today. The purpose of this study was to assess the dental age (DA) and skeletal age (SA) of children with FAS and compare them with matched controls.

The samples of 90 children diagnosed with FAS and 90 controls were matched for age, gender, and social class. The mean chronological age (CA) of the FAS subjects was 8.95 years, with the controls slightly older at 9.04 years. This difference was not significant. Dental maturity was determined by assessing the stage of tooth formation and SA assessment was made from hand–wrist radiographs for the patients and controls by assigning a SA and comparing it with standard plates. The means and standard deviations of CA and DA for the stages of calcification were calculated and the Pearson ranked order correlation coefficient was applied to measure the associations between skeletal maturity indicators and DA. *t*-tests were used to test for group differences between independent groups, and paired *t*-tests to determine paired group differences.

This study provided evidence of a positive association between DA and SA in both the FAS children and the controls. The data suggest that both DA and SA may be a reflection of general somatic growth.

It must be acknowledged that growth of individuals is often irregular, when any norms of development based on central tendencies and variabilities of healthy children are applied. Some aspects of growth and development for healthy children may show a variable pattern of growth. Therefore, correlation of these aspects of growth and development will often not show the degree of correlation that theoretically exists between different areas of growth and development. A more complete appraisal of the entire skeleton and an evaluation of the entire dentition, rather than just the mandibular teeth, might improve the correlation between the variables.

Introduction

The hallmarks of foetal alcohol syndrome (FAS) have been catalogued, quantified, and refined over the years and many investigators have established that the most consistent consequences of maternal drinking during pregnancy are pre- and post-natal growth deficiency as well as brain and craniofacial abnormalities (Hanson *et al.*, 1976, 1978; Chernoff, 1977; Clarren and Smith, 1978; Clarren *et al.*, 1978; Streissguth *et al.*, 1980; Sulik *et al.*, 1986; Kotch and Sulik, 1992; Coles, 1994; Weston *et al.*, 1994).

The typical characteristics of FAS are:

1. Facial abnormalities, such as microcephaly, a narrow forehead, micrognathia, maxillary hypoplasia, a flat midface, narrow palpebral fissures, a short and small nose, a long upper lip with a narrow vermillion border, and diminished or absent philtrum and epicanthal folds;
2. Central nervous system dysfunction with mental retardation ranging from mild to severe;
3. Growth deficiency that presents as lower weight and height at birth persisting into the post-natal period;
4. Various cardiovascular and skeletal abnormalities (Jones and Smith, 1973).

The purpose of this study was to investigate the relationship between dental age (DA) and skeletal age (SA) to several measurements of growth between a cohort of children with FAS and matched controls.

Subjects and methods

Ethical considerations

The protocol was approved by the Research Ethics Committee of the University of Stellenbosch. Written informed consent was obtained from the principal of each participating school and the parents or guardians of each child. Access to the participants of the study was made initially by letter to the participating school principals and parents. An introduction by the researcher, the basic aims and objectives of the study, what participating in the study would involve, what examinations were to be carried out,

and how long the examination would take were fully explained in their native language. It was emphasized that strict confidentiality would be maintained at all times and that the results of the study would be presented in a manner that ensured anonymity. Once a signed informed consent form was received for each child, arrangements were made for the clinical examinations to be carried out at a time convenient to the participants and schools. Children were brought to the School for Oral Health Sciences, Faculty of Health Sciences at Tygerberg Hospital. Following the dental and skeletal assessment, specific interventions for any child (subject or control) found to have medical problems related to the study were carried out at the Avalon Treatment Centre, Foundation for Alcohol-Related Research, Department of Genetics, University of Cape Town, where full specialist and psycho-social support was provided. This included the provision of growth hormone (GH) therapy in some cases. Children with dental, orthodontic, and oral-health-related problems were treated at the School for Oral Health Sciences, at the University of Stellenbosch. In addition, each child received an individual oral health report within 3 months of completion of the survey, with appropriate advice. Written informed consent was obtained from the parents of the children whose photographs were used for reporting purposes.

Diagnosis and screening of FAS cases

The diagnosis of the FAS subjects was carried out by active case ascertainment in the Wellington community in the Western Cape (Institute of Medicine, 1996). In this case assessment, no attempt was made to aggregate the individual traits of pre-natal alcohol exposure into lesser, non-syndrome diagnoses commonly referred to as 'foetal alcohol effects', 'alcohol-related birth defects', or 'alcohol-related neurodevelopmental deficits'. Only FAS (or not FAS), the most accurate and rigorous diagnosis, was used (May *et al.*, 2000). Specific FAS diagnostic components of the Institute of Medicine (1996) were used for the initial screening: (1) facial and other dysmorphology, (2) diminished structural growth for age, (3) developmental (intelligence and social skills) delay, and, when possible, (4) confirmation of maternal alcohol consumption. Data for each of these components were independently collected, quantified, and analysed. Dysmorphology, growth, and developmental data for children were collected by means of a two-tier screening method after normative data were assessed for this particular population (May *et al.*, 2000). Four teams, each containing two specialists, one expert dysmorphologist and one South African physician trained in FAS diagnosis, worked independently but simultaneously and used standardized assessment criteria to examine all children in sub A (first grade) classrooms. One author (SN) was part of the group that was trained and calibrated in FAS diagnosis.

Twelve elementary schools in the community ($n = 992$, sub A children) were assessed. In terms of the previous Population Registration Act in South Africa, people were classified according to ethnic groups of 'black' (African), 'coloured', 'Indian', and 'white'. The sample in this study comprised only coloured schoolchildren and screening proceeded as follows: (1) A complete dysmorphology examination was undertaken of each of the initial 406 schoolchildren from classrooms in six of the rural and urban schools to determine both local normative growth parameters and possible FAS dysmorphology relative to the United States National Centre for Health Statistics charts. (2) Data for these 406 children were analysed. All the children with suspected classic FAS had height, weight, and occipito-frontal circumference measurements below the 10th centile for one of the three measurements. (3) With local parameters assessed, cut-off points were set for implementing the two-tier screening system. (4) All of the 586 children in sub A classrooms in the remaining six schools received tier I screening (height, weight, and occipito-frontal circumference). Children whose measurements were below the 10th centile on occipito-frontal circumference or on both height and weight were referred for the complete examination (tier II) by the dysmorphology teams. Finally, 220 of the remaining children met these criteria and were referred for complete examinations. Therefore, 626 children (63 per cent) received full dysmorphology examinations.

Every child receiving the complete screening (tier II) was examined by two of the physician teams. They measured the child's occipito-frontal circumference; palpebral fissure length; philtrum length; inner and outer canthal distance; and other indicators such as abnormalities in joints, heart function, and palmar creases. The findings were recorded on data forms, and the physicians in each team verified each other's finding. All physicians were 'blinded' from any prior knowledge of the child or mother. Once seen by one team, the child was directed to another blinded team that repeated the examination and measurements as a reliability check. Mean differences between dysmorphologists' measurements for the first 25 children were checked and were insignificant for key measures: inner canthal distance (0.22 cm), interpupillary distance (0.29 cm), and palpebral fissure length (0.04 cm). Interrater reliability was later assessed for 194 matched pairs with the square root of the Pearson product moment correlation (r). The results were 0.91 for inner canthal distance, 0.85 for interpupillary distance, and 0.84 for philtrum measurements. After the dysmorphology examination had been completed by two teams, a child was assigned a preliminary diagnosis of 'not FAS', 'deferred', or 'FAS' based on the qualified FAS check-list and all clinical findings. Children with a deferred diagnosis had the appearance and some anomalies of FAS with growth delay, but developmental test and maternal interview data were required for a final diagnosis. Only those with the classic FAS phenotype and measurements well below the fifth centile for all measurements received a preliminary FAS diagnosis. The present study sample consisted of 90 children diagnosed with FAS and 90 controls matched for age, gender, ethnicity, and social class.

Dental maturity was determined by assessing the stage of tooth formation. Dental maturation was assessed from panoramic radiographs using the seven-tooth system (Demirjian *et al.*, 1973) expressed as DA in months. The methods most widely used to determine SA are those of Tanner *et al.* (1973) and Greulich and Pyle (1959). Studies have compared the two methods and found minor, insignificant differences between them (Milner *et al.*, 1986; Cole *et al.*, 1988; King *et al.*, 1994). However, the Greulich and Pyle method appeared to be less time-consuming and was therefore the preferred method. SA assessment was undertaken using hand–wrist radiographs for the subjects and controls. Each child was assigned an SA and this was compared with standard plates (Greulich and Pyle, 1959).

Descriptive statistics were obtained by calculating the means, standard deviations, minimums, and maximums of chronological age (CA), DA, and SA for the stages of calcification. The Pearson ranked order correlation coefficient was applied to measure the associations between skeletal maturity indicators, DA, and CA. The *t*-test was used to determine group differences between the two groups, and the paired *t*-test to test for differences between paired groups. Statistical significance was at the 5 per cent level ($P < 0.05$).

Results

Demography

The mean CA of the FAS subjects was 8.95 years with the controls slightly older at 9.04 years. This difference was not significant ($P = 0.634$). There was an equal gender distribution.

Dental age

The mean CA, DA, and dental delay score (DDS, DA−CA) of the subjects and controls are shown in Tables 1 and 2. The group difference between the subjects and controls for the DDS was examined in boys and girls separately.

The DDS for the FAS boys (mean = 0.17) was significantly lower than the DDS for the controls (mean = 0.90, $P < 0.001$). For both groups of boys the score was positive, suggesting that their DA was higher than their CA, but this difference was much more pronounced in the control group. The DDS was highly significant within the control group of boys ($P < 0.001$), but not significant among the FAS boys ($P = 0.23$).

The DDS for FAS girls (mean = −0.64) was not significantly different from the DDS for the controls (mean = −0.21). Both groups of girls had a negative DDS, suggesting that their CA was higher than their DA. This difference was slightly more pronounced in the FAS girls. The DDS was highly significant in the FAS group of girls ($P = 0.001$), but not significant among the control girls ($P = 0.34$).

Skeletal age

The mean CA, SA, and skeletal delay score (SDS) of boys and girls, both subjects and controls, are shown in Tables 3 and 4, respectively. Again, the group difference between subjects and controls was examined separately for boys and girls. The SDS for the FAS boys (mean = −22.56) was significantly higher than the SDS of the controls (mean = −9.51, $P < 0.001$). The score for both the FAS and the control boys was negative, suggesting that their CA was higher than their SA. The SDS was highly significant for both the FAS and control boys ($P < 0.001$).

The SDS for the FAS girls (mean = −10.71) was significantly higher than that for the controls (mean = −0.68, $P < 0.001$). As for the boys, CA was higher than SA (negative scores). SDS was highly significant within the FAS girls ($P < 0.001$), but not significant within the control girls. The entire sample's SA against CA in months is shown in Figure 1. Figure 2 shows the same SA against CA for the boys only. In Figure 2, the isochron line clearly shows that SA lags behind CA in the FAS children.

Discussion

Dental development

GH, insulin-like growth factor 1 (IGF-1), as well as thyroid and steroid hormones are all crucial for development during early childhood. The capacity of tissue to accept and utilize hormones is dependent upon factors via appropriate receptors as well as the amount of GH-binding protein and IGF-1-binding protein that are important for hormonal transport,

Table 1 Chronological age, dental age, and dental delay score in years in subjects with foetal alcohol syndrome (FAS) and controls (boys).

	FAS				Control			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Chronological age	8.92	1.21	7.08	11.17	9.06	1.32	7.17	12.67
Dental age	9.10	1.24	7.50	12.80	9.96	1.47	7.60	12.80
Dental delay score	0.17			0.90				
P-value	<0.001							

Table 2 Chronological age, dental age, and dental delay score in years in subjects with foetal alcohol syndrome (FAS) and controls (girls).

	FAS				Control			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Chronological age	8.97	1.33	7.17	12.00	9.02	1.33	7.17	12.83
Dental age	8.33	1.09	7.10	11.60	8.79	1.43	7.40	12.30
Dental delay score	−0.64				−0.21			
P-value	0.1323							

Table 3 Chronological age, skeletal age, and skeletal delay score in months in subjects with foetal alcohol syndrome (FAS) and controls (boys).

	FAS				Control			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Chronological age	107.09	14.58	85.00	134.00	108.71	15.85	86.00	152.00
Skeletal age	84.53	14.69	48.00	120.00	99.20	15.65	72.00	132.00
Skeletal delay score	−22.56				−9.51			
P-value	<0.001							

Table 4 Chronological age, skeletal age, and skeletal delay score in months in subjects with foetal alcohol syndrome (FAS) and controls (girls).

	FAS				Control			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Chronological age	107.60	15.97	86.00	144.00	108.18	15.93	86.00	154.00
Skeletal age	96.89	12.99	69.00	120.00	107.50	13.86	82.00	144.00
Skeletal delay score	−10.71			−0.68				
P-value	<0.0001							

SD, standard deviation. Skeletal delay score = skeletal age − chronological age. *P*-value = test statistic of the skeletal delay score of FAS.

and consequently their tissue uptake that results in growth activity (Myllärniemi *et al.*, 1978). IGF-I, IGF-II, and IGF-binding proteins are important modulators of foetal growth and development (Singh *et al.*, 1994). Most studies on maternal alcohol exposure have revealed reduced circulating IGF-I levels in the foetus (Halmesmaki *et al.*, 1989; Sonntag and Boyd, 1989; Breese and D'Costa, 1993). It is generally assumed that orofacial development follows the predominant growth pattern of the body, which is controlled by the same endocrine system (Demirjian *et al.*, 1973). Independent of each other, different examiners have reported delayed dental maturity in children with or without impaired hormonal status or as part of a syndrome (Loevy, 1983; Hägg and Matsson, 1985; Pelsmaekers *et al.*, 1997; Nykänen *et al.*, 1998). Several forms of cell perturbations have been associated with alcohol ingestion during pregnancy. Diminished maxillofacial development and inhibition of cell regulation *in vivo* and *in vitro* have been described in children presenting with FAS (Shibley and Pennington, 1997; Maier *et al.*, 1999).

Dental maturity

The aim of this study was to assess dental maturity in terms of CA compared with DA, from panoramic radiographs, using the widely accepted seven-tooth method (Demirjian *et al.*, 1973). This method is a reliable criterion for determining dental maturation and was chosen as the most precise and accurate evaluation of DA because its criteria consists of distinct details based on anatomical definitions of dental maturation. One of the reasons for the widespread acceptance of this maturity scoring method system is its universal application in comparative studies of a similar

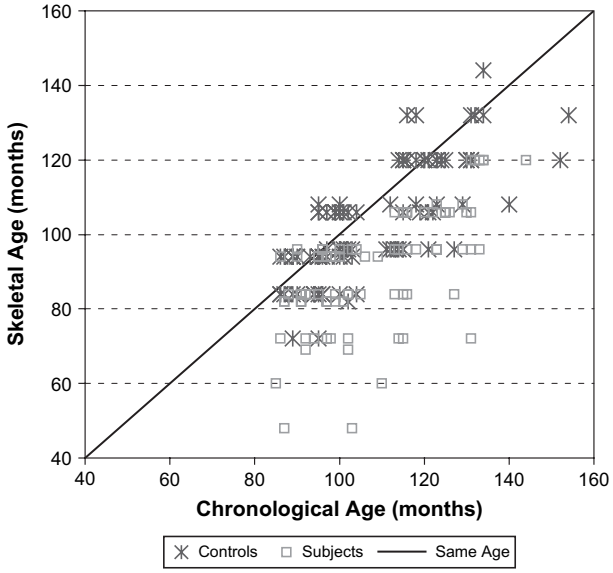

Figure 1 Chronological age versus skeletal age in months for the entire sample (n = 180).

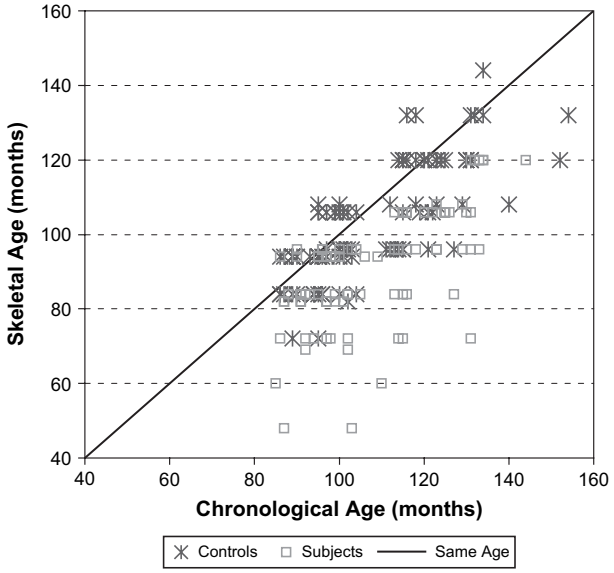

Figure 2 Chronological age versus skeletal age in months for boys only.

nature. It was hypothesized that as growth is delayed in FAS children, there should be a concomitant dental maturity delay.

DA: FAS versus control. The DDS for FAS boys was significantly lower than that for the controls (Table 1), but that for the FAS girls was not significantly different from their controls (Table 2). Interestingly, only the boys had a positive DDS (DA higher than CA), with that in the control group being more pronounced (mean = 0.90). Since dental maturation has been shown to be delayed in children with delayed development (Garn *et al.*, 1959, 1965; Keller *et al.*, 1970; Pirinen, 1995), this is not a surprising finding in this study. The mean DA indicated that FAS and control boys matured earlier than FAS and control girls. Differences between DA and CA (DDS) were noted for both boys and girls, and there was a significant difference (positive) in the control boys ($P < 0.001$) and (negative) in the FAS girls ($P = 0.001$).

Skeletal maturity

SA: FAS versus control. In this study the mean age of skeletal maturity indicated that the FAS and control girls matured earlier than the boys. This concurs with findings of several reports of children in the general population (Björk and Helm, 1972; Grave and Brown, 1976; Fishman, 1982; Hägg and Taranger, 1982). Differences between SA and CA were noted for both boys and girls and there were significant differences in the SDS in all the FAS children (boys and girls, $P < 0.001$) but only in the control boys ($P < 0.001$). The mean SDS in the FAS subjects was much higher than the mean score in the controls, indicating that in the FAS children, CA was much higher than the SA.

Cole *et al.* (1988) explained that there are three sources of discrepancy between SA and CA: natural variations between individuals in their rates of skeletal maturation, systematic error inherent in the method used to assess SA, and differences between the various examiners. It is possible that the first two sources may have influenced the discrepancy between SA and CA. Examiner error was probably least likely since the SA assessment was performed by two examiners simultaneously, and the reproducibility test showed a very strong coefficient of reliability ($r = 0.99$).

The natural variation in SA between the subjects whose radiographs were used to set the standard plates (Greulich and Pyle, 1959) and the sample in this study may be in part associated with environmental factors and racial differences, the sample in the Atlas having been derived from a white, north European ancestry, and some hand–wrist radiographs were not exactly comparable with the standard plates.

SA versus CA

All the children in the sample had a SA significantly lower than their CA (Tables 3 and 4). The present study showed a significant mean reduction in the SA of this sample when compared with the group used to compile Greulich and Pyle's atlas in the 1950s. Several studies have been published on the relevance of this atlas to different populations in the 50 years since it was published.

Lewis *et al.* (2002) showed a significant mean reduction in the SAs of a sample of Malawian children when compared with Greulich and Pyle's atlas. Van Rijn *et al.* (2001) and

Groell *et al.* (1999) found the atlas to be still applicable in Dutch Caucasian and central European children, respectively, but Mora *et al.* (2001) reported significant differences in skeletal maturation between American children of European and African descent. Rikhasor *et al.* (1999) showed that Pakistani children of both genders were a few months in advance of their skeletal development compared with the atlas until puberty, but fell behind post-puberty. Loder *et al.* (1993) investigated black and white children in the geographical area from which the atlas originated and found minor changes; however, the studies of both Loder *et al.* (1993) and Ontell *et al.* (1996) comparing SA and CA in healthy children were limited by the lack of using age-adjusted normal standards for height and weight to verify normal growth in their subjects. The cause of the markedly reduced SA in the present study is not clear. While this may be related to poor nutrition, no relationship could be found between poor nutrition and the degree of skeletal delay. Two other studies of delay in skeletal development (Mackay, 1952; Fleshman, 2000) also suggested poor nutrition as being the cause of skeletal delay, but they were unable to show statistically significant support for this hypothesis. The findings of a reduced SA in this study may imply that care should be exercised when using the atlas of Greulich and Pyle (1959), and it may become necessary to develop a new bone age atlas for sub-Saharan Africa, addressing the diversity of ethnic groups that would enhance our ability to determine skeletal maturation with accuracy, reliability, and consistency.

Address for correspondence
Professor Sudeshni Naidoo
Department of Community Oral Health
University of the Western Cape
Private Bag X1
Tygerberg 7505
South Africa
E-mail: suenaidoo@uwc.ac.za

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