Dental and oro-facial features of Foetal Anticonvulsant Syndrome

Hetal Shukla, Alison Meldrum, Dorothy Boyd

ABSTRACT

AIM: Emerging evidence suggests dental/oro-facial anomalies are features of Foetal Anticonvulsant Syndrome (FACS) and have an impact on quality of life. Currently there is limited research on these, and no Aotearoa New Zealand data on FACS overall. This study aimed to collect national data on the dental and oro-facial features of FACS.

METHODS: A participatory model was utilised; a questionnaire was developed and distributed to FACS-affected families via the Foetal Anticonvulsant Syndrome New Zealand (FACS NZ) organisation. Open-ended questions were asked about: socio-demographics, anticonvulsant drug regime at the time of pregnancy, characteristic features of the affected child, including oro-facial function, dental/oro-facial anomalies, and dental history.

RESULTS: Valproate was the most prescribed anticonvulsant during pregnancy. Oro-facial functional abnormalities in speech, swallowing, and eating were identified in 70.4% of the FACS population. Dental anomalies were reported by 81%, the most common being dental crowding, followed by tooth discolouration and microdontia.

CONCLUSION: Dental and oro-facial anomalies were reported commonly in the Aotearoa New Zealand FACS population, laying foundation for further research. Recognition of these features assists in FACS diagnosis, early referral, and improved management of FACS patients. The need for FACS education for women of reproductive age requiring anticonvulsant therapy, in Aotearoa New Zealand, was identified.

First introduced in the mid-1800s, anticonvulsant agents (also known as anti-epileptic or anti-seizure drugs) are among the most commonly prescribed medications for epilepsy, manic-depressive (bipolar) disorder, mood stabilisation, neuropathic pain, migraine prophylaxis and mental health conditions.[1] The teratogenicity of these drugs was first established when congenital malformations were seen in infants of mothers who had first-generation anticonvulsant drugs during pregnancy. Subsequent animal studies confirmed the increased risk of developmental anomalies in the offspring of treated females.[2] It is now known that the use of anticonvulsants during pregnancy increases the risk of foetal abnormalities by 2–3%, and this rises to 10% with the use of valproate (a second-generation anticonvulsant) in particular.[3] However, the chronic and complex nature of epileptic and psychiatric disorders pose clinical challenges in the management of women of child-bearing age, as treatment with single or multiple anticonvulsant agents is often required to decrease medical complications during pregnancy.[4]

Foetal Anticonvulsant Syndrome (FACS) is the overarching term for a pattern of multiple developmental anomalies associated with prenatal exposure to one or more anticonvulsant agents.[5] FACS can be sub-categorised based on the specific attributing anticonvulsant; for example, valproate is known to cause "foetal valproate syndrome."[6]

There are three broad categories of the characteristic features of FACS—dysmorphic facial features, irregularities of the organs and limbs, and cognitive impairment/autism spectrum disorder (ASD).[7] Dysmorphic facial features such as trigonocephaly, medial eyebrow deficiency, epicanthic eyelid folds, flat nasal bridge, shallow philtrum, and lip irregularities have been reported in FACS cases, particularly with foetal exposure to phenytoin, valproate, and carbamazepine.[8] There is emerging evidence that dental and oro-facial anomalies may also be features of FACS. Three studies have investigated the incidence of dental agenesis of the permanent dentition,[9] and one case of an enamel defect on a mandibular incisor tooth has been reported.[10] One study explored phenytoin and valproate in mono- and polytherapy and found an association between in utero exposure and decreased maxillary and mandibular height and length, reduced posterior cranial base length and a decrease in the relative anteroposterior positions of the maxilla and mandible. This study also identified mild maxillary hypoplasia.[11] In a retrospective

study of 91 children born to mothers who used anticonvulsant drugs during their pregnancies, dental anomalies were observed in 48.4% of all the children. The most frequent dental anomalies were enamel hypoplasia, delayed eruption, and malocclusion.[12]

Facial structures are vital for functions such as respiration, mastication, swallowing and speech, and have psychological and social impacts that can affect the quality of life. Investigating oro-facial problems associated with FACS could allow their recognition as part of the syndrome, facilitate diagnosis, and may also give grounds to support access to specialist dental care (such as paediatric dental and orthodontic care) for affected children.[13] The knowledge, expertise and resources of the community affected by a condition are often key to successful research, particularly in the study of medical problems with limited data.[14] To date, there is very limited knowledge on the dental and oro-facial features of FACS, and there has been no Aotearoa New Zealand research on FACS. This study aimed to collect Aotearoa New Zealand-based data on the dental and oro-facial features observed in individuals with FACS.

Methods

Ethical approval was granted by the Human Research Ethics Committee, University of Otago (reference H19/031).

Parents or caregivers with at least one child with FACS were invited to complete a simple, open-ended questionnaire to obtain information, opinions, and experiences on their child's dental and oro-facial features. The questionnaire was pre-tested with a family with two children diagnosed with FACS, and subsequently amended and made available to the wider FACS community for completion over a 4-week period between May 2019 and June 2019. A reminder email and link were sent 2 weeks after the initial notification.

The parents/caregivers were recruited via the FACS New Zealand (FACS NZ) organisation through a link directing them to the questionnaire on Qualtrics^{XM} (an online survey tool). The survey invitation was sent out by the president of FACS NZ via the closed Facebook page and email, reaching approximately 65 families with FACS-affected children. Responses were analysed using a Microsoft Excel spreadsheet.

The questionnaire (Table 1) was divided into six sections to gather information on socio-demographics, anticonvulsant drug regime, characteristic FACS features, oro-facial function, dental/oro-facial anomalies, and dental history. There was a combination of open-ended and tick-box questions, with free-text sections for elaboration. An additional section for further comments and/or concerns was also included.

Results

A total of 35 responses were received. Of these, seven responses were blank, and one had been repeated, leading to eight responses being disregarded. A total of 27 valid responses were included and analysed, representing a 41.5% response rate.

Socio-demographics

The responses were about individuals with FACS aged between 4–27 years at the time of the study. Twenty-four responses were from caregivers whose child had a confirmed FACS diagnosis, and three responses reported a provisional FACS diagnosis. Three responses did not specify the age at which the child was diagnosed with FACS. Among respondents with confirmed FACS, the mean age of FACS diagnosis was 8.5 years (range: 2 months–23 years). The sex ratio of FACS-affected children was evenly divided, with 13 females (48.2%), 12 males (44.4%) and 2 unspecified (7.4%). Four responses did not specify the child's ethnicity. Of the remaining 23 responses, 100% identified as being of NZ European descent.

Anticonvulsant drug regime

There was a 100% response rate to the question regarding the mother's anticonvulsant drug regime during pregnancy. Twenty-two mothers (81.5%) were on monotherapy (valproate, carbamazepine, or lamotrigine), and five (18.5%) were on polytherapy during their pregnancies (Table 2). Valproate was the most common anticonvulsant prescribed to mothers on a monotherapy regime and was present in all polytherapy regimes, followed by lamotrigine, which was reported in both mono- and polytherapy regimes.

Characteristic FACS features

The most commonly reported FACS characteristic was dysmorphic facial features (92.5%), followed by cognitive impairment (88.9%). The type of anticonvulsant regime (mono- or polytherapy) during the pregnancy did not

influence the features reported in the child. Cognitive impairment/ASD, either alone or in combination with another established feature category, was reported in 19 of the 22 children with *in utero* exposure to a single anticonvulsant agent.

Oro-facial function assessment

Nineteen responses (70.4%) indicated an oro-facial functional problem with speaking, swallowing, or eating, or a combination of these. Seven reported no functional problems and one did not answer the question. All three problem areas were reported in one child exposed to valproate in monotherapy. In contrast, functional problems were not reported with prenatal exposure to carbamazepine. All children exposed to valproate, either in mono- or polytherapy regimes presented with one or more functional problem (Table 3).

A speech problem was the most common functional issue (16 cases). Of these, two responses stated that their child was non-verbal, one reported a severe stammer, and seven reported the need for ongoing speech and language therapy. All children with speech difficulties also had autism spectrum disorder.

Swallowing was the next most commonly reported functional concern (10/19). Parents/caregivers reported that their child "choked easily", had "uncoordinated swallowing" or "required food in small pieces". Five reported eating problems. In the free-text section, children were described as "messy" or "slow" eaters. Two reported the need for soft foods due to sensory processing disorders secondary to FACS. Seven responses stated the child had a tongue-tie at birth and had breastfeeding difficulties. Of these, two reported that feeding and swallowing improved following tongue-tie release.

Dental and oro-facial anomalies

One or more dental anomalies were reported in 22 responses (Table 4). Crowding, discolouration of the teeth and microdontia (teeth smaller than normal) were the most frequently reported concerns, respectively. Of those who reported dental discolouration, one reported diagnosis of dental hypomineralisation and two of dentinal sensitivity. Other less frequently reported anomalies included missing teeth, spacing between the teeth, abnormalities in the eruption of primary teeth and position of permanent teeth, and macrodontia (teeth larger than normal). Monotherapy or polytherapy anticonvulsant drug regimens during pregnancy did not affect the presence of dental anomalies.

In the free-text section, three cases stated a professional diagnosis of mid-facial hypoplasia, congenital micrognathia, and increased overbite and midline diastema, respectively. Orthodontic treatment needed for correction of jaw misalignment and malocclusion was reported in 30% of the responses. There were no reports of congenital cleft lip and/or palate; however, four responders mentioned that their child had an unusually high palatal vault, three of these children having problems with eating and swallowing.

Of the 27 responses, 22 provided an answer to the questions about dental history. Twelve caregivers (55%) reported that their child was unable to cope in the dental setting, including one who reported the need for general anaesthesia for all dental care. The reasons given included anxiety (n=7), autism spectrum disorder (n=3) and a severe gag reflex (n=1). Ten caregivers (45%) reported that their child could cope well in the dental setting. Of these, two stated their child required a support person in proximity. All of these children also had diagnosed autism spectrum disorder.

Discussion

This study was the first to collect Aotearoa New Zealand data on the FACS patient group. The results showed that the characteristic FACS features were rarely reported in isolation and that dysmorphic facial features and dental anomalies were commonly reported by parents/caregivers of children with FACS. The most common dental anomaly reported was dental crowding, followed by tooth discolouration and morphological variation in the size of the teeth. When parents/caregivers reported one or more oro-facial functional abnormalities, the most common problem was related to speech. Over half reported that their child could not cope well in the dental setting, indicating that dental specialist care may be needed for a large proportion of this group.

Dental anomalies in number, size, morphology, and position of the teeth in individuals with FACS may be explained by the effect of anticonvulsant agents in the first trimester, as dental development commences at week six *in utero*.[15,16] Missing or extra teeth, termed hypodontia or hyperdontia, respectively, can occur due to biological disturbances in the formation of the

Table 1: Questionnaire distributed to parents/caregivers of children with FACS in Aotearoa New Zealand.

Section	Question	Question type	Free-text section
Socio-demographics	Date of birth Gender Ethnicity	Write answer	No
	Age of FACS diagnosis	Write age in year/months	No
Anticonvulsant drug regime	Anticonvulsant drugs taken by mother during pregnancy	List medication(s)	No
Characteristic FACS features	1. Irregularities of the eyes, ears, lips, and nose 2. Irregularities of organs or limbs 3. Cognitive impairment/ autism spectrum disorder 4. Other	Tick relevant, explain if "other"	Yes
Oro-facial function assessment	Have you noticed any problems with the way your child eats, speaks, or swallows?	Open-ended	Yes
Dental/oro-facial anomalies	Have you noticed any problems with your child's teeth?	Open-ended	Yes
	Have you noticed any differences in the appearance of your child's face and/or teeth compared with other children of his/ her age?	Open-ended	Yes
	Does your child have a history of a cleft lip and/or palate?	Yes/No	No
Dental history	Does your child attend routine dental care?	Yes/No	No
	Does your child cope well in the dental setting?	Yes/No	Yes
	Additional comments	Open-ended	Yes

Table 2: Features of FACS reported and the mother's anticonvulsant drug regime during pregnancy.

FACS feature	Monotherapy			Polytherapy	
	Valproate	Carbamazepine	Lamotrigine	Valproate, lamotrigine	Valproate, lamotrigine, levetiracetam
DFF	2	-	-	-	-
IO/L	-	-	-	-	-
C/ASD	1	-	-	1	
DFF + IO/L	-	-	-	-	1
DFF + C/ASD	5	-	1	1	-
IO/L + C/ASD	1	-	-	-	-
DFF + IO/L + C/ASD	11	1	-	2	-

DFF: dysmorphic facial features
IO/L: irregular organs/limbs
C/ASD: cognitive/autism spectrum disorder

Table 3: Functional problems reported in FACS individuals and the mother's anticonvulsant drug regime during pregnancy.

Functional Problem	Monotherapy			Polytherapy	
	Valproate	Carbamazepine	Lamotrigine	Valproate, lamotrigine	Valproate, lamotrigine, levetiracetam
Eating	1	-	-		-
Speaking	3	-	1	1	-
Swallowing	1	-	-	-	-
Eating + speaking	2	-	-	1	-
Eating + swallowing		-	-	-	-
Speaking + swallowing	7	-	1	-	-
Eating + speaking + swallowing	1	-		-	-
No functional problem	4	1		1	1

Table 4: List and number of dental anomalies reported by parents/caregivers of children affected by FACS.

	Dental anomaly	Number of responses
Number of teeth	Supernumerary teeth	4
	Missing teeth	2
Size and form of teeth	Macrodontia	1
	Microdontia	5
	Morphological variation	4
Appearance of teeth	Discoloured teeth	7
	Hypomineralisation of teeth	1
Position of teeth	Crowding of teeth	8
	Spacing between teeth	3
No anomaly	No dental anomaly	5

dental lamina during the early weeks of the embryonic period.[15] Mutations of the MSX1 and PAX9 genes have also been associated with tooth agenesis in humans, and animal investigations have found an association between the absence of these genes due to environmental stimuli such as medications, and the presence of multiple craniofacial anomalies.[17] Furthermore, dental agenesis and morphological variations have been attributed to change in the Wingless/Integrated (Wnt) signaling (that is essential for tooth development) as a result of histone deacetylase inhibition by anticonvulsant drugs.[1,9,18] Tooth discolouration was commonly reported in our study (32%), which correlates with previous research, where enamel hypoplasia was frequently seen in children to mothers on anticonvulsant drugs. Morphological variation, supernumerary teeth and hypodontia were also identified, and in keeping with our findings.[12] Enamel hypoplasia presents clinically as white, yellow, or brown discolouration with surface roughness or pitting.[19]

Crowding and spacing of the dentition in FACS children has not been previously reported; however, it has been reported that the relative dimension of the maxilla and mandible may influence the positioning and eruption pattern of the dentition.[20] Micrognathia and mid-facial hypoplasia have been reported in FACS cases for a number of years alongside other dysmorphic facial features.[21–23] Deformities in the mid-face are attributed to aberrations in genes involved in signaling pathways, such as Wnt, fibroblast growth factor (FGF) and transforming growth factor-Beta (TGF *beta*), due to the teratogenic action of anticonvulsants.[24] A professional diagnosis of micrognathia and midfacial hypoplasia was reported by parents/caregivers in two questionnaire responses. In both cases, the child also had dental crowding. Furthermore, one-third of the responses mentioned that orthodontic treatment was required for management of malocclusion. As the questionnaire did not specifically ask about jaw position and orthodontic treatment, this figure is likely to be an underestimate.

Oro-facial functional abnormalities were common (70.4%), and these may present secondary to delayed development and cognitive function or may be due to anatomical variations of the tongue, palate, and lips. In this

study, all children with speech difficulties also had diagnosed ASD—a possible primary cause for their functional problem. Concomitantly, a cleft palate or a high palatal vault may lead to problems in articulation of words and a hyper-nasal sound in the speech.[25] Ankyloglossia (tongue-tie) has been reported in approximately 27% of FACS cases and may affect speech, feeding and swallowing.[26] From the questionnaire, congenital ankyloglossia was reported in approximately 26% of the responses, all of whom stated they also had trouble feeding their child.

This study has allowed better understanding about the prescription of anticonvulsants in Aotearoa New Zealand over the last two decades. Valproate was the most prescribed anticonvulsant agent among the study group, despite extensive literature on its risk of foetal harm.[27] Among responses, the youngest child with FACS was four years of age; the eldest, 27 years. Both were prenatally exposed to valproate and reported oro-facial anomalies. The responses indicated valproate, carbamazepine, and lamotrigine were the three main anticonvulsants prescribed in pregnancy in this Aotearoa New Zealand group. The reported oro-facial features were consistent with the known teratogenic effects of valproate and carbamazepine previously cited in literature[28] and provide valuable information on lamotrigine, as children exposed to this drug also reported abnormalities of the facial features, congenital malformations, cognitive problems, and dental/oro-facial anomalies.

Two parents/caregivers stated that they were unaware of the foetal risks from valproate during pregnancy. As this question was not specifically asked, it is possible that more mothers were unaware, and that there may be a need for improved education and information on FACS when females of childbearing age are prescribed anticonvulsants. The current International League Against Epilepsy (ILAE) guideline for optimal management of women of childbearing age on anticonvulsant medication begins preconception and involves monitoring through all three trimesters, with follow-up assessments to approximately 6 weeks postpartum. Furthermore, clinical visits with the neurologist with open discussions, along with blood workups for anticonvulsant drug levels and communication between the mother's neurologist and obstetrician, are key elements to effective management of mothers on anticonvulsants.[29]

There are several strengths and limitations to consider in this study. This study utilised an online questionnaire, as this provided an efficient means of distribution and collection of information from the FACS patient group. A sampling bias is acknowledged as with any online means of distribution; only those with internet access, active Facebook accounts and regular access to email could partake in the study. Undercoverage of the target population is therefore possible. The questionnaire was comprised of open-ended questions using lay terminology and data was interpreted by grouping together similar responses. For example, parents/caregivers who described their child's teeth as "packed together, "overlapping" or "overcrowded" were all categorised in the "crowded dentition" category. While measurement and researcher errors can be introduced in qualitative research, a participatory approach from the outset was critical, as patients and their parents/caregivers are experts in their condition and there is very limited research currently available on the dental and oro-facial features of FACS. While a recall bias is plausible as many responses relied on the parents/caregivers' recollection of the past (for example the drug regime during pregnancy and age of FACS diagnosis), it is argued that such questions could be answered accurately with the aid of previous medical prescriptions or documentation. The fact that all responders identified as NZ European means further work is needed to reach and gain the experiences of Māori, Pasifika and families from other ethnicities affected by FACS. As this questionnaire targeted families with children affected by FACS and members of FACS NZ, the inferences from this study are relevant to all patients affected by FACS in Aotearoa New Zealand. Due to privacy, FACS NZ does not maintain a database of families involved in the organisation. While the exact number of those invited to participate in this study was unknown, an estimate of 65 families were sent the email and invited to take part, reflecting a response rate of approximately 42%.

In 2017, the House of Commons of the United Kingdom issued a debate pack report on FACS. While it acknowledged "facial and skull malformations" from anticonvulsant use during pregnancy, there was no mention of dental and oro-facial abnormalities.[3] Furthermore, the current FACS diagnostic criteria model is based on the characteristic features of FACS (dysmorphic facial features, congenital

malformations, cognitive impairment/ASD) and does not include dental and oro-facial features.[30] Our study provides preliminary data on FACS in Aotearoa New Zealand, gives insight into the dental and oro-facial features in affected individuals, and indicates that there is a need to consider dental anomalies as well as oro-facial features, rather than facial features only, in FACS patients. Further research in this area is therefore encouraged.

The results from this study can be utilised in many ways. Firstly, they can assist in the development of an examination proforma or checklist that can enable recognition of dental and oro-facial anomalies in FACS individuals by dental and medical practitioners. This may be advantageous in FACS diagnosis or data collection for further research, and/or provide a basis for early referral and improved management for this patient group, especially as improved dental function can significantly improve quality of life. Secondly, the study draws attention to anticonvulsant drug prescription in Aotearoa New Zealand and suggests the need for better education for women of childbearing age regarding the foetal risks with anticonvulsant use during pregnancy. Finally, this study provides a foundation for research on FACS in Aotearoa New Zealand as, to date, there has been no national research with this patient group.

COMPETING INTERESTS
Nil. This study was funded by the New Zealand Dental Association Sir John Walsh Scholarship as part of the Bachelor of Dental Surgery with Honours programme.

ACKNOWLEDGEMENTS
The authors would like to sincerely acknowledge the support of Denise Astill, president of the Foetal Anticonvulsant Syndrome New Zealand (FACS NZ) organisation, who enabled this research to reach the FACS community. We also gratefully thank the families affected by FACS for not only participating in this study, but also for their words of appreciation that encouraged this manuscript.

AUTHOR INFORMATION
Hetal Shukla: Dentist, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.
Alison Meldrum: Associate Professor and Head of Discipline of Paediatric Dentistry, Department of Oral Sciences, University of Otago, Dunedin, New Zealand.
Dorothy Boyd: Senior Lecturer, Department of Oral Sciences, University of Otago, Dunedin, New Zealand.

CORRESPONDING AUTHOR
Hetal Shukla: Dentist, Faculty of Dentistry, University of Otago, Dunedin, New Zealand.
E: hetalshukla.31@gmail.com

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Appendices

Original questionnaire distributed to parents/caregivers of children with FACS in Aotearoa New Zealand.

Dear Parent/Caregiver

As you may be aware, there are many known features associated with the Foetal Anticonvulsant Syndrome (FACS). Although limited, there is current evidence in literature that suggests that abnormalities related to the face, mouth and teeth may also be associated with FACS. At the University of Otago, we are conducting research of these associations and would like to know about your observations and first-hand experience. Please fill in the questionnaire below relating to any features of the face, mouth and teeth that you have observed in your child. If you have more than one child with FACS, please complete a separate questionnaire for each child. Your answers are valuable to our research and will be used solely for the purpose of directing further research.

1) Personal information (child):
Date of birth:.....
Gender:.....
Ethnicity:.....

2) When was your child diagnosed with Foetal Anticonvulsant Syndrome?
Child's age:.....

3) Please state the name(s) of the anticonvulsant medications that you were taking during the pregnancy:
.....
.....
.....
.....

4) Please tick the relevant features of FACS currently seen in your child:
Irregularities of the eyes, ears, lips and nose
Irregularities of organs or limbs
Cognitive disabilities/Autism spectrum disorder
Other
Please explain if you have ticked Other:
.....
.....

5) Have you noticed any problems with the way your child eats, speaks or swallows?
Please explain what you have noticed:
.....
.....
.....

6) Have you noticed any problems with your child's teeth?
Please explain what you have noticed:
.....
.....
.....

7) Have you noticed any differences in the appearance of your child's face and/or teeth compared with other children of his/her age?
Please explain what you have noticed:
.....
.....
.....

8) Does your child attend routine dental care?

Yes

No

9) Does your child cope well in the dental setting?

Yes

No

If you have answered no, please briefly explain the problems encountered during your child's dental visit:

.....

.....

.....

10) Does your child have a history of a cleft lip and/or palate?

Yes

Please explain:

.....

.....

No

11) Additional comments or concerns relating to your child's dental and facial features:

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Thank you for participating in this questionnaire.
We appreciate your time and your responses are very valuable to our research.