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The Aetiology of Hypodontia: The prevalence, severity and location of hypodontia within families.

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This paper has been submitted for consideration for inclusion in a Supplement to Archives of Oral Biology. This Supplement arises from a series of papers given at an International Workshop on Oral Growth and Development held in Liverpool on November 26-28, 2007. The papers to be submitted consist of a series of review and new concept papers to be followed by papers outlining new work in each of the areas covered by the reviews.

Abstract

Aims: Previous studies have indicated that hypodontia has a significantly higher prevalence in the relatives of affected individuals than in the general population. This study aims to examine further the roles of genetic and environmental factors in the aetiology of hypodontia by investigating the relationship between the severity and distribution of hypodontia between family members, and any discernable effect of maternal health during pregnancy and birth weight.

Methods and Results: 117 first degree relatives of 41 index patients were examined clinically and radiographically to identify the presence, severity and location of hypodontia. Both siblings and parents of index patients had a higher prevalence of hypodontia than the general population. The number and location of missing teeth was not related to the number and location of missing teeth in parents or siblings. The expression of hypodontia within a family was not affected by maternal health during pregnancy.

Conclusions: The variation found in the expression of hypodontia within families suggests that its occurrence is not solely determined by genetic factors, but epigenetic and environmental factors probably also are important. This finding is consistent with a multifactorial aetiology for this condition.

Key words:

Hypodontia, aetiology, family study

Introduction

Hypodontia, the congenital absence of one or more teeth is a common anomaly of dental development, its population prevalence being some 4-5% in British Caucasians (1-3). Structured family studies, including the work of Brook (2, 3), Grahnen (4), Chosack (5) and Arte (6), have investigated its prevalence in relatives of patients with hypodontia and found it substantially exceeds that of the general population. Prevalence values have ranged from 11.8% to 39% for first degree relatives (i.e. parents and siblings). However, there is little reliable evidence available regarding an association in severity and distribution of hypodontia between family members. Furthermore, in the published family studies it is not clear if the family members were analysed as independent subjects. If specific formulae for examining clusters of family members are not used, then this may introduce bias into the results (7).

Following a prevalence and family study (2, 3), Brook proposed a single multifactorial model to link hypodontia, microdontia, supernumeraries and megadontia. The model is based on an underlying continuous distribution of tooth size and combines polygenic and environmental influences. The theory that the mode of transfer of hypodontia is not entirely genetic is supported by the variable expression of hypodontia in monozygotic twins. Boruchov (8), Moller et al (9) and Townsend et al (10) found substantial differences in the severity and location of hypodontia in monozygotic twins or triplets and suggested that environmental factors may be important in the expression of the trait.

The aim of the present study was to gain further information concerning the roles of genetic and environmental factors, including the role of maternal factors, in the aetiology of hypodontia by investigating the association in number and location of hypodontia amongst relatives of affected index cases.

Materials and Methods

Ethical approval was obtained for the study from the National Health Service (NHS) Trusts in Sheffield and North Derbyshire where the patients were treated. 117 first degree relatives (parents and siblings) of 41 index patients, the initially presenting patients with hypodontia in each affected family, presenting at the Charles Clifford Dental Hospital, Sheffield and the Chesterfield and North Derbyshire Royal Hospital, were examined clinically and radiographically. The presence, severity and location of hypodontia were recorded for all teeth in the dentition apart from third molars. Hypodontia was observed in most positions within the dentition, apart from upper central incisors, lower canines and lower first molars.

Patients were selected who had hypodontia, were white Caucasian, aged over 9 years so that radiographically all permanent forming tooth germs except third molars would show evidence of calcification, and who had no recognisable syndrome associated with hypodontia. None of the first degree relatives examined had a recognisable syndrome associated with hypodontia. The prevalence of hypodontia in the general British Caucasian population was used as a control.

An orthopantogram (OPT) was taken for each patient to be included in the study. If records of previous extractions could not be obtained verbally with assurance, then information was requested from their General Dental Practitioner. Information regarding birth weight of offspring/siblings and illnesses suffered by the mother during pregnancy were obtained by direct questioning.

The radiographic films were examined using a standard light box and the location and number of missing teeth were recorded and compared with the dental history forms to determine the congenitally missing teeth.

For reproducibility fifty of the radiographic films were re-examined under the same viewing conditions four weeks later and the number and location of congenitally missing teeth were recorded for a second time by the same examiner. Comparisons of prevalence, severity and location of hypodontia within each family were conducted using a combination of SPSS (version 6, SPSS Inc.) and MLwinN (University of Bristol Centre for Multilevel Modelling).

Results

Siblings of index cases

All siblings had an equal chance of being an index patient since they theoretically have the same chance of receiving the genes that determine the trait. It therefore did not matter which child with missing teeth in a family was used as the index case.

There were 33 index patients (11 males and 22 females) whose siblings were examined for hypodontia. Of the 9 siblings with hypodontia, all originated from different families (Table 1). Some of the siblings without hypodontia were from the same family, for example the index patient of one family had 3 siblings with a full complement of teeth. Estimation of the prevalence and its variance therefore required the use of specific formulae for cluster sampling, where the clusters (i.e. siblings from the same family) were of unequal sizes. Using this method, the average proportion of siblings (within the same family) who also have hypodontia was 8.37% to 29.13% with a p value of 0.1875, variance of 0.0027, and a

standard of error of 0.0519. Hence the 95% confidence interval for the estimated prevalence would be 0.1875 +/- 2 x 0.0519 = (0.0837, 0.2913).

The prevalence of hypodontia amongst British subjects had been found to lie between 4% and 5% (1, 3). Since the above confidence interval exceeds these values this would appear to suggest a significantly greater prevalence rate of hypodontia in siblings of index patients than in the general population.

Parents of index patients

Results for parents from 38 families were available. For 5 of these families only one parent was examined; however the formula for cluster sampling accounted for this, the cluster sizes being either +1 or +2.

Of the 20 parents of index patients who also had hypodontia, each came from a different family (Table 1). Using the same method as for the siblings, the proportion would be 20.38% to 37.58% with a p value of 0.2898, variance of 0.0018 and a standard error of 0.0430. The 95% confidence interval for the estimated prevalence is (0.2038, 0.3758). Again, this is far greater than 4% - 5%, suggesting a larger prevalence of hypodontia in parents of children with hypodontia than in the general population.

Impact of parental hypodontia on the proportion of affected offspring

In the families included in this analysis, data were obtained for both parents. Logit/Probit analysis was used since the data is non-parametric and hence linear regression is not appropriate.

The results of the analysis showed that the coefficient/standard error (of coefficient) was 1.86. The proportion was 5% to 10% estimated as p=0.65 when a parent had hypodontia compared with p=0.42 when the parent did not have hypodontia. This suggests that there is 'slight evidence' of an increase in the proportion of offspring with hypodontia in families when a parent has hypodontia, relative to families where neither parent has hypodontia.

Associations in numbers of missing teeth amongst families

9 families had more than one affected child. Kendall's rank correlation gave a non-significant p value of 0.378, suggesting no association. A similar picture was seen when affected parents were compared to their affected offspring.

The mean values for missing number of teeth in the offspring were 4.92 (affected parents) and 4.68 (unaffected parents). The Mann-Whitney U test gave a non-significant p-value of 0.985, providing no evidence of a difference in the number of missing teeth in affected offspring with a parent who had hypodontia, compared to affected offspring whose parents did not have hypodontia.

Association of location

When comparing locations of missing teeth amongst siblings, similarity tests were performed. It was found that 52.8% of siblings had hypodontia in similar locations to each other. Using the Logit/Probit analysis, it was found that the location of hypodontia in affected offspring did not appear to be dependent on the location of hypodontia in affected parents.

Environmental effects during intra-uterine development

Using Logit/Probit analysis, there was no significant difference in the proportion of siblings affected, depending on illnesses suffered by the mother during pregnancy.

The mean birth weights of offspring with and without hypodontia were also compared, accounting for the fact that offspring belonging to the same family were not independent and needed to be grouped together (Table 2). Following a multi-level analysis and using the MLwiN package (University of Bristol Centre for Multilevel Modelling), it was found that there was no significant difference in birth weight between offspring with and without hypodontia, the difference in the mean values being -0.04 (p-value = 0.999).

Discussion

This study explored relationships between the index patients with hypodontia and their first degree relatives in the number and location of missing teeth. As a consequence, statistical analysis was more involved because each member of the same family had to be treated as non-independent when making inter-family comparisons. Other studies in the literature appear to have treated each family member as being independent, therefore comparisons with other studies are more difficult and the results are not directly comparable.

The results (although not significant) are in agreement with other family studies (3-6) in that the prevalence of hypodontia in first degree relatives is higher than that of the general population, but not as high as expected if an autosomal dominant single gene were entirely responsible (Tables 3 and 4). In some families the index patients were the only members found to have hypodontia, whereas in other families, siblings and parents were also affected. This finding does not fit well with exclusive single gene determination of hypodontia. The

most likely explanation for the prevalence of hypodontia in first degree relatives is that a number of genes are involved, at different loci. Some of the genes already identified are MSX 1, PAX 9 and AXIN 2 (11), although MSX 1 and PAX 9 at least are not consistently found in all families with hypodontia (12, 13). Recently, isolated hypodontia in two families has been described in association with a missense mutation in the EDA gene; affected individuals show no other signs of ectodermal dysplasia (14). There is evidence to suggest that PAX 9 and MSX 1 interact during tooth development (11). It is the interaction of such genes, in a certain environment, that results in hypodontia. Hence the aetiology can be described as being multifactorial and may account for the different teeth missing in affected individuals with the same mutation, as seen in the families reported by Rasool et al. (14).

When looking at the association of the number of absent teeth amongst relatives of the same family, no statistically significant evidence was found either for parents or siblings of index patients. Thus other modifying genes, epigenetic and environmental factors may be important in determining the expression of this trait.

With regard to the association of the location of hypodontia in members of the same family, the similarity amongst offspring (52.8%) may indicate that hypodontia affecting different tooth types is caused by different genetic factors. However, this leaves 47.2% of offspring expressing hypodontia in different locations to each other, suggesting that combinations of genes, epigenetic and environmental factors are important in determining expression of hypodontia.

Continuous traits such as height and tooth size typically have a multifactorial mode of inheritance. Brook (3) and Bailit (15) suggested hypodontia is an example of a ‘quasi-

continuous' trait with a threshold mechanism (Figure 1). The accepted explanation of discontinuous multifactorial variation rests on the assumption that there is an underlying scale of continuous variation, this being, in the case of hypodontia, tooth size. The distribution curve of relatives appears to be to the left of that of the general population in Figure 1. The position of an individual on the scale depends upon a combination of numerous genetic and environmental factors. Proportionally more family members of index patients exceed the threshold for tooth agenesis. The model also suggests that first degree relatives of index patients will have reduced mean tooth dimensions compared to the general population, even if they do not have hypodontia. Another study by our group, using similar patient samples and measuring tooth dimensions using image analysis in both relatives with and without hypodontia, showed smaller tooth size than controls even in unaffected first degree relatives (16).

Maternal Effects

Maternal health during pregnancy and birth-weights of offspring were used as measures of maternal effects on hypodontia expression.

Maternal health is thought to be an important intra-uterine factor and abnormal tooth development has been reported in cases of rubella, Rhesus-incompatability and other metabolic diseases (17, 18). Any effect of maternal health on hypodontia is only likely to be seen in those teeth that form early in development, as those whose formation is initiated after birth are unlikely to be influenced by the intra-uterine environment. This study did not find any influence of maternal illnesses on the proportion of siblings with hypodontia.

Bailit and Sung (19) used birth weight as a measure of inter-uterine conditions and considered that most of the variance in birth weight is accounted for by environmental factors with maternal genotype having less influence. Weak evidence is available for the influence of birth weight on the congenital absence of teeth (8, 20). The current study did not find any differences in birth weight between siblings with or without hypodontia. Between family variation was taken into account in the analysis used since birth weights of siblings were compared within a family and not between families. It is not clear that this was also the case in the previous studies mentioned. The analysis used also allowed the influence of the presence of hypodontia in the parents to be examined; the presence of hypodontia in the parent had no bearing on the mean birth weight of their children.

The results of this study support the multifactorial mode of inheritance of hypodontia proposed by Brook (2). The estimated prevalence of hypodontia in first degree relatives of hypodontia patients was higher than that of the general population, and there was slight evidence of an increase in the proportion of offspring affected if the parent had hypodontia. The likelihood of hypodontia occurring in first degree relatives varied from family to family, indicating that multiple genes are involved in hypodontia. However, the impact of environmental factors in the aetiology of hypodontia was clear from the expression of hypodontia in the studied families:-

1. There was no evidence for a similarity between the mean numbers of missing teeth amongst affected offspring of the same family.
2. Affected parents did not appear to have a similar number of missing teeth to their affected offspring.

3. The location of missing teeth in affected offspring did not appear to be dependent on the location of missing teeth in affected parents. When locations were compared between affected offspring, the probability that hypodontia occurred in the same specific location was only 52.8%, with 47.2% of affected siblings having hypodontia in different locations to each other.

Nevertheless, the intra-uterine environment did not appear to have a strong impact upon the expression of hypodontia within susceptible families, as maternal illnesses during pregnancy, maternal hypodontia and the birth weight of the child did not appear to alter its chance of having hypodontia. This may be in part due to the limited potential for the intra-uterine environment to affect the formation of later developing teeth within the dentition, such as the premolars.

It is recognised that congenital absence of teeth is only part of the full phenotype (Fig 1) and the parallel study of McKeown et al (16) showed that in families in which some individuals had marked hypodontia, even relatives with a complete dentition had significantly smaller teeth than controls.

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Table 1. Summary of prevalence of hypodontia in first degree relatives

	No. of individuals	No. of individuals with hypodontia	95% confidence interval for prevalence
Siblings	48	9	8.37% - 29.13%
Parents	69	20	20.38% - 37.58%

Table 2. Mean birth weights (BW) of offspring (kg)

	Parent with hypodontia	Parent without hypodontia
Mean BW of offspring with hypodontia	7.188	7.449
Mean BW of offspring without hypodontia	7.184	7.445
Mean BW of all offspring	7.186	7.447

Table 3. Comparison of prevalence of hypodontia in **siblings** with other family studies.

	Total no. of sibs	No. with hypodontia	Prevalence
Brook (3)	80	28	35%
Grahnen (4)	223	58	26%
Chosack et al (5)	371	55	15%
Current study	48	9	8% - 29%

Table 4. Prevalence of hypodontia in **parents** of index cases.

	Total no. parents	No. with hypodontia	Prevalence
Brook (3)	74	24	32%
Grahnen (4)	107	44	41%
Chosack et al (5)	449	42	9%
Current study	69	20	20 – 38%

Figure legends

Figure 1. Brook (2) proposed a model for the aetiology of dental anomalies based on the normal distribution of tooth size. This figure with the first degree relatives curve shifted to the left accounts for the higher frequency of hypodontia in first degree relatives of hypodontia patients as well as their smaller tooth size (16).