Developmental enamel defects in tuberous sclerosis: a clinical genetic marker?

N Flanagan, W J O'Connor, B McCartan, S Miller, J McMenamin, R Watson

Abstract

Ten probands with tuberous sclerosis (TS) and 20 first degree relatives were examined for evidence of pitted enamel hypoplasia; 100% of TS patients had pitting, compared to 65% of relatives and 72% of controls. We found that 70% of TS cases had more than 14 pits per person compared with only 5% of relatives and 4% of controls; 85% of relatives and 84% of controls had fewer than six pits per person. Our results confirm that significantly increased numbers of dental enamel pits are found in persons with TS compared to controls. These results suggest that examination for the presence or absence of dental enamel pits is not a useful screening test for first degree relatives to detect otherwise unsuspected subjects with tuberous sclerosis. However, the lack of pits in first degree relatives in our study is probably largely because none of the relatives appeared to carry the TS gene.

(J Med Genet 1997;34:637-639)

Keywords: tuberous sclerosis; teeth; dental pits

Tuberous sclerosis (TS) is an autosomal dominant disorder characterised by hamartoma formation in many organs. The prevalence of the disease is about 1 per 10 000. Genetic linkage analysis studies have indicated that approximately half of all TS families show linkage to chromosome 9q34 and half to chromosome 16p13. Positional cloning efforts are now under way in several centres to attempt to find the TSC1 gene. The TSC2 gene on chromosome 16 has recently been isolated. Seventy percent of cases appear to arise as new mutations, but this rate may be falsely high as the manifestations of the disease may be subtle. There are a few families with documented non-penetrance. Several families have been described in which two affected children were born to parents who appeared to be completely normal after thorough evaluation. The more clinical or special tests which are carried out on apparently unaffected first degree relatives, the more likely that some abnormality will be detected. Previous studies have established that dental enamel pitting is common in TS. This study was performed to assess the value of dental examination as a screening test for first degree relatives of apparent sporadic TS cases.

Patients and methods

Thirty-one subjects from 11 families of TS patients participated, comprising 11 TS cases, 10 probands and 20 relatives. All probands fulfilled the diagnostic criteria for definite TS and none of the relatives had any features to suggest a diagnosis of TS. Ten TS patients underwent dental examination, the remaining child being uncooperative. Both parents were available for examination in seven families. Six parents were not examined because they were unavailable for examination, edentulous, or had died. The median age of the TS cases was 24 years (range 5-37) and of the first degree relatives 41 years (range 8-65). Twenty-five controls, median age 23 years (range 21-31), all of whom were young adult dentists, dental students, or dental nurses, also participated in the dental part of the study. Any teeth which had been restored or crowned were excluded. Permanent and deciduous teeth were examined. TS patients and their first degree relatives also underwent full skin examination (including Wood's light examination) and renal ultrasound.

The technique used in the dental examination was modified from that of Mlynarczyk. All dental examinations were carried out by the same registered dental hygienist using a dental chair, dental light, and a sharp dental explorer. The labial surfaces of the 12 anterior teeth (incisors and canines) were given a standard dental prophylaxis, following which a disclosing solution (stain) was applied using a sponge. The teeth were dried using a cotton roll. The teeth were explored carefully with the probe

<table>
<thead>
<tr>
<th>Probands</th>
<th>Relatives</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Mean</td>
<td>No</td>
</tr>
<tr>
<td>1.95</td>
<td>19</td>
<td>0.67</td>
</tr>
<tr>
<td>0.80</td>
<td>20</td>
<td>0.26</td>
</tr>
<tr>
<td>1.40</td>
<td>20</td>
<td>0.46</td>
</tr>
<tr>
<td>0.85</td>
<td>20</td>
<td>0.08</td>
</tr>
<tr>
<td>1.00</td>
<td>20</td>
<td>0.11</td>
</tr>
<tr>
<td>1.72</td>
<td>20</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table 1: Prevalence of dental pitting in TS probands compared with relatives and controls

Table 2: Mean numbers of pits, and numbers of teeth, for each tooth type examined in TS cases, first degree relatives, and controls

Department of Dermatology, St James's Hospital, St James's Street, Dublin, Ireland
N Flanagan W J O'Connor R Watson

Department of Oral Surgery, Oral Medicine and Oral Pathology, Dublin Dental Hospital, Dublin, Ireland
B McCartan

Department of Radiology, St James's Hospital, St James's Street, Dublin, Ireland
S Miller

Department of Neurology, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland
J McMenamin

Correspondence to: Dr Flanagan, Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK.

Received 21 June 1996
Revised version accepted for publication 8 April 1997

*Probands v relatives, p<0.0005, IRR=2.3.
**Probands v controls, p<0.0005, IRR=2.7.

16 parents, and four sibs. All probands fulfilled the diagnostic criteria for definite TS and none of the relatives had any features to suggest a diagnosis of TS. Ten TS patients underwent dental examination, the remaining child being uncooperative. Both parents were available for examination in seven families. Six parents were not examined because they were unavailable for examination, edentulous, or had died. The median age of the TS cases was 24 years (range 5-37) and of the first degree relatives 41 years (range 8-65). Twenty-five controls, median age 23 years (range 21-31), all of whom were young adult dentists, dental students, or dental nurses, also participated in the dental part of the study. Any teeth which had been restored or crowned were excluded. Permanent and deciduous teeth were examined. TS patients and their first degree relatives also underwent full skin examination (including Wood's light examination) and renal ultrasound.

The technique used in the dental examination was modified from that of Mlynarczyk. All dental examinations were carried out by the same registered dental hygienist using a dental chair, dental light, and a sharp dental explorer. The labial surfaces of the 12 anterior teeth (incisors and canines) were given a standard dental prophylaxis, following which a disclosing solution (stain) was applied using a sponge. The teeth were dried using a cotton roll. The teeth were explored carefully with the probe

Table 1: Prevalence of dental pitting in TS probands compared with relatives and controls

Table 2: Mean numbers of pits, and numbers of teeth, for each tooth type examined in TS cases, first degree relatives, and controls

Maxilla
Central incisor 1.95         0.67  33  0.22  50
Lateral incisor 0.80        0.26  31  0.62  50
Canine          1.40        0.46  35  0.40  50
Mandible        0.85        0.08  38  0.02  50
Central incisor 1.00        0.11  38  0.08  50
Lateral incisor 1.72        0.29  38  0.12  50
found to have significantly increased numbers of dental enamel pits when compared with controls (IRR=2.7, p<0.0005) and when compared with relatives (IRR=2.3, p=0.0005). There was no significant difference in the overall number of dental enamel pits between relatives and controls (IRR=1.1, p=0.45).

Six of the nine TS patients (66%) who underwent renal ultrasound showed multiple bilateral angiomyolipomata and this finding was not seen in any of the 20 first degree relatives. All but one proband showed cutaneous manifestations of TS and none of the first degree relatives had any cutaneous manifestations of TS.

Discussion

Pits were first described by Hoff et al. in 1975 in a series of six patients with TS. Since then several studies have shown that dental enamel pits are a common finding in TS. Roach et al. included dental enamel pits as a tertiary feature in the diagnostic criteria for TS. Our finding of 100% prevalence of dental enamel pits in probands correlates with the study by Mlynarczyk. Thus dental pits may be the commonest manifestation of TS and therefore a helpful marker in the diagnosis of this disease. In comparison, the second most frequent manifestation of TS is renal angiomyolipomata, detected in 67% of TS patients in this and other studies.

The pathogenesis of pitted enamel hypoplasia in TS is not understood. Previous studies suggest that the pits extend to the amelodontinal junction. The pits appear to result from a reduction in the amount of enamel matrix formed. This may be because of a primary defect in odontoblasts, or in ameloblasts, or may be the result of defective interaction between odontoblasts and ameloblasts.

Dental enamel pits are not specific for TS. They are present in the general population although the exact prevalence is unclear. They are also associated with other abnormalities of amelogenesis, including pitted amelogenesis imperfecta, vitamin D dependent rickets, epidermolysis bullosa dystrophica, pseudohyoparathyroidism, and tricho-dento-osseous syndrome. These conditions are easily differentiated by the presence of additional dental defects such as pulp and root deformities, with the exception of pitted amelogenesis imperfecta. By contrast, the enamel defects in TS are mainly seen on the labial surfaces of the teeth away from the gingivae, in areas that rarely become carious. Water fluoridation may cause

Table 3 Previous studies looking at dental enamel pitting in tuberous sclerosis probands, relatives, and controls

<table>
<thead>
<tr>
<th>No</th>
<th>% with pits</th>
<th>No</th>
<th>% with pits</th>
<th>No</th>
<th>% with pits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probands</td>
<td>35 typical TS</td>
<td>71</td>
<td>21&lt;11 y</td>
<td>76</td>
<td>6 deciduous teeth</td>
</tr>
<tr>
<td></td>
<td>10 atypical TS</td>
<td>10</td>
<td>29&lt;11 y</td>
<td>100</td>
<td>23 permanent teeth</td>
</tr>
<tr>
<td>Relatives</td>
<td>68</td>
<td>13</td>
<td>—</td>
<td>9</td>
<td>563</td>
</tr>
<tr>
<td>Controls</td>
<td>50</td>
<td>14</td>
<td>250</td>
<td>9</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Used no dental stain and a fine probe.
†Used a dental plaque disclosing solution and a dental explorer.
‡Used no stain and a ball end probe.
Developmental enamel defects in tuberous sclerosis

We wish to thank Dr Alan Kelly from the Department of Community Health and General Practice, Trinity College Dublin, for his assistance in the statistical analysis in this study.