Can salivary composition and high flow rate explain the low caries rate in children with familial dysautonomia?

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Abstract

Purpose: Extremely low caries rate and increased major salivary gland flow rate have been previously reported in children with familial dysautonomia (FD). The purpose of this study was to explore the possibility that, in addition to increased salivary flow, children with FD have alterations in their salivary components, which may suggest an explanation to their low caries rate.

Methods: Whole unstimulated and stimulated saliva samples were collected from 13 children with FD who were found to be caries free, and from 28 age- and ethnic-matched healthy children, 15 caries-free children and 13 caries-affected children. The electrolyte and protein content of the unstimulated saliva and the microbial count and buffering capacity of the stimulated saliva were determined.

Results: Children with FD had the highest salivary flow rate and the lowest levels of mutans streptococci and lactobacilli, as well as the lowest concentration of chloride, magnesium, total protein and IgA. Healthy caries-affected children displayed the highest mutans streptococci and lactobacilli levels and lysozyme concentration, concomitantly with the lowest potassium and calcium concentrations.

Conclusions: The results of this investigation suggest that the caries-free state in FD may be associated with high salivary flow rate, while in healthy children, low caries rate may be associated with high salivary calcium concentration.(*Pediatr Dent.* 2002;24:581-586)

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Familial dysautonomia (FD) is an autosomal recessive disorder that exclusively affects children of Jewish Ashkenazi origin. Clinical features such as impaired pain perception, skeletal deformities, recurrent pneumonias, orthostatic hypotension, progressive degeneration of tongue fungiform papillae and taste buds, impaired taste and smell, and multiple dysautonomic crises are the result of hereditary autonomic and sensory neuropathy (HASN) type III.[1] In a previous study, we have shown that children with FD are rarely affected by dental caries, despite their poor oral hygiene habits.[2] In subsequent studies, it was shown that children with FD have an increased major salivary gland flow rate and submandibular/sublingual gland hyperfunction at the acinar and ductal level, possibly due to denervation supersensitivity.[3,4] FD is the first disease to cause basal salivary gland hyperfunction. Although the association of low salivary flow rate with increased caries activity is well known,[5,6] there is no published evidence for the influence of high salivary flow rate on caries activity. Among the many caries-related salivary parameters are buffering capacity, mutans streptococci (MS) and lactobacilli (LB) levels,[5,7] and concentrations of IgA, lysozyme,[8] calcium, and phosphorus.[9,10] However, correlations between single salivary protective constituents and caries rate are difficult to find.[8]

The purpose of this study was to analyze various salivary parameters in a group of children with FD and in 2 age- and ethnic-matched control groups (ie, caries affected and caries free).

Methods

The study population consisted of 41 Ashkenazi Jewish children divided into 3 groups: (1) The study group consisted of 13 patients with FD. (2) The control caries-free (CCF) group consisted of 15 healthy subjects. (3) The control caries-affected (CCA) group consisted of 13 healthy subjects. All 3 groups were pair matched by age and gender and came from a similar socioeconomic background. Patients with FD, who were randomly recruited from the FD patient database of 2 of the authors (EM and NG), fulfilled the diagnostic criteria for the disorder,[11] and the diagnosis was confirmed in each by one of the authors (NG). A detailed dental history was obtained with emphasis on oral hygiene habits and dietary characteristics, especially sugar intake and snack frequency. In addition, oral hygiene was assessed by the amount of bacterial plaque present on the teeth. Each of these parameters was qualified as "good," "moderate," or "poor." Specifically, up to 1 snack per day was considered a "good" dietary habit, 2 to 3 "moderate," and 3 or more "poor." Past exposure to fluoride was qualified as "significant" (persistent use of fluoridated drinking water and/or fluoride supplements) or "nonsignificant." After the receipt of informed consent by the parents and no more than 6 months prior to the saliva collection, patients and controls underwent a comprehensive oral examination by one of the authors (EM) who is an experienced pediatric dentist. The examination was a routine procedure in the examiner's private office and included bitewing radiographs.

Saliva collections were carried out between 9 AM to 12 PM. Subjects were instructed to refrain from eating, drinking, and tooth brushing for a minimum of 90 minutes before saliva collection. Unstimulated whole saliva was collected by expectoration into an ice-chilled tube for 5 minutes and its flow rate was calculated using gravimetric methods (assuming a specific gravity of saliva of 1.0) and expressed as ml/min.[12] For electrolyte and protein content measurements, these samples were frozen at -20°C and thawed shortly before analyses.

Stimulated whole saliva was collected following 5 minutes of paraffin chewing and immediately used for caries activity tests, for which commercially available methods (Orion Diagnostica, Espoo, Finland) were used. As children with FD were unable to chew effectively, reliable flow rates could not be obtained. Salivary buffering effect was assessed using the Dentobuff strip method, which defines a final pH of saliva of <4.5 as low (0), a pH of 4.5 to 5.5 as intermediate (1), and a pH >5.5 as high buffering activity (2).[13,14] Salivary MS were tested with Dentocult SM Strip mutans test and their level was determined as scores 0, 1, 2, and 3 corresponding to <10,[4] 10^4-10,[5] 10^5-10,[6] and $>10^6$ colony-forming units (CFU), respectively.[15] Salivary LB were analyzed with Dentocult-LB dip-slide test, which classifies counts of <10,[3] 10,[3] 10,[4] 10,[5] and $\geq 10^6$ CFU as scores 0, 1, 2, 3, and 4.[16,17]

IgA and lysozyme were assayed by radial immunodiffusion on Kallestad Endoplate and Quantiplate kits, respectively (Kallestad Laboratories Inc, Austin, Tex). Calcium and phosphorus were determined with a Hitachi 717 automated analyzer using Boehringer Mannheim kits. Magnesium was measured with a Perkin-Elmer model 2380 Atomic Absorption Spectrophotometer. Amylase was measured by the blocked PNG7 method using Raichem kit (RAI, San Diego, Calif). Sodium and potassium were measured with the IL 743 Flame Photometer (Instrumentation Laboratories Company, Lexington, Mass). Chloride was measured on a CMT 10 Chloridometer (Radiometer, Copenhagen, Denmark). Protein was determined according to Lowry.[18]

Statistical analyses were performed using one-way ANOVA procedures. Since multiple comparisons were carried out, the improved Bonferroni procedure was adopted.[19]

Table 1. Mean Values (SD) of Salivary Parameters

Parameter	FD*	CCF†	CCA‡
Unstimulated flow rate (ml/min)	0.90 (0.66)	0.47 (0.27)	0.56 (0.22)
Buffering capacity (U)	0.4 (0.7)	0.7 (1.3)	0.9 (1.0)
Mutans streptococci (U)	0.2 (0.6)	1.5 (1.1)	2.2 (1.0)
Lactobacilli (U)	0.5 (0.9)	1.3 (1.5)	3.1 (1.4)
Sodium (mEq/l)	9.8 (3.2)	13.0 (5.2)	11.3 (3.0)
Chloride (mEq/l)	11.0 (3.8)	18.0 (5.9)	13.2 (3.6)
Potassium (mEq/l)	20.3 (5.7)	21.4 (4.1)	16.0 (3.4)
Calcium (mg/dl)	2.2 (1.7)	2.5 (1.4)	1.5 (0.6)
Phosphorus (mg/dl)	13.3 (7.2)	13.6 (3.7)	11.0 (3.4)
Magnesium (mg/dl)	0.3 (0.1)	0.7 (0.5)	0.5 (0.3)
Total protein (g/l)	1.1 (0.6)	1.7 (0.6)	1.9 (2.4)
IgA (mg/dl)	2.4 (1.5)	3.4 (0.3)	3.2 (0.2)
Lysozyme (mg/ml)	5.5 (6.4)	4.1 (1.8)	9.8 (8.0)
Amylase (KU/l)	77.9 (54.4)	89.0 (93.2)	62.1 (49.4)

*FD=familial dysautonomia
†CCF=control caries free
‡CCA=control caries active

Results

The FD group was comprised of 10 boys and 3 girls aged 5 to 17 years (mean=10.5 years). The CCF group consisted of 11 boys and 4 girls (mean age=10.6 years), and the CCA group consisted of 10 boys and 3 girls (mean age 9.9 years). There was no statistically significant difference in the mean age of the groups. All were similar in terms of past exposure to fluoride, which was mostly "nonsignificant." The CCF and CCA children were similar in oral hygiene practices and dietary habits: 50% scored "moderate," 25% "good," and 25% "poor." Approximately 60% of children with FD had "poor" oral hygiene and altered dietary habits, 30% "moderate" and 10% "good." Most patients in the FD group were caries free, except 1 girl who had small carious

lesions on 2 proximal surfaces of adjacent primary molars and 1 boy who had 4 amalgam restorations on occlusal surfaces of primary and permanent molars. Therefore, the dental caries status of the FD group was considered similar to the CCF group. The mean overall DMF-def rate in the CCA group was 9.7±3.3.

The values of the measured salivary parameters are shown in Table 1 and the results of the statistical analysis in Table 2. Children with FD differed significantly from all controls combined together in terms of higher salivary flow rate and lower MS and LB counts, as well as decreased chloride, magnesium, total protein, and IgA concentrations. Although both FD and CCF groups had a similar dental caries status (FD had an extremely low caries rate), salivary flow rates were higher in FD, while MS, chloride, and IgA concentrations were significantly lower. Saliva from the CCA group differed from that of FD and CCF groups regarding lower potassium and calcium concentrations and higher MS, LB, and lysozyme levels. Potassium and calcium were lower in the CCA group compared to the CCF group while MS and magnesium were higher in the CCA group, compared to the FD group. The CCA group had a consistently higher LB level and lysozyme concentration than FD and CCF groups. Output per minute of all analyzed salivary constituents did not differ significantly between the 3 groups.

Table 2. Statistical Comparison of Salivary Parameter between Study Groups

Groups compared	FD vs CCA	FD vs CCF	FD+CCF vs CCA	CCA vs CCF	FD vs CCA+CCF
Unstimulated flow rate	NS	*P*<.02	NS	NS	*P*<.01
Mutans streptococci	*P*<.0001	*P*<.0005	*P*<.002	NS	*P*<.0001
Lactobacilli	*P*<.0001	NS	*P*<.0001	*P*<.001	*P*<.005
Lysozyme	*P*<.005	NS	*P*<.001	*P*<.005	NS
Chloride	NS	*P*<.001	NS	NS	*P*<.01
Potassium	NS	NS	*P*<.005	*P*<.005	NS
Calcium	NS	NS	*P*<.02	*P*<.02	NS
IgA	NS	*P*<.01	NS	NS	*P*<.005
Magnesium	*P*<.0005	NS	NS	NS	*P*<.001
Total protein	NS	NS	NS	NS	*P*<.05

NS=not significant
No statistical significance was found between the study groups in the values of buffering capacity, sodium, phosphorus, and amylase

Discussion

The primary goal of the present study was to characterize a salivary profile that could be responsible for the extremely low caries level found in children with FD. The most striking finding was the significantly increased salivary flow rate in FD compared to the combined CCA and CCF groups. As previously reported, salivary gland hyperfunction in FD, as manifested by the increased flow rate, may be due to denervation supersensitivity of the partially denervated salivary glands.[3] Increased salivary flow rate may significantly contribute to oral health by optimizing cleansing and increasing buffering power and degree of saturation with respect to tooth minerals.[6,8,20] Increased salivary flow rate was the only "caries protective" parameter found in FD as compared to the combined CCA and CCF groups. Although no statistically significant difference in salivary flow rate was found between the FD and the CCF groups, there was a trend towards higher flow rate in FD. Therefore, it may be assumed that, despite poor oral hygiene and altered dietary habits,[2] children with FD are protected from dental caries by their high salivary flow rate.

The CCF group had the highest salivary calcium and phosphorus concentrations. However, statistical significance was found only when the CCF group was compared with the CCA in respect to calcium concentration. The role of calcium and phosphorus in dental remineralization is well known,[5] and their concentration in whole stimulated saliva reflects their level in plaque.[21] High levels of calcium and phosphorus in whole and parotid saliva were found to be associated with a low dental caries rate.[9,10,22] However, in other studies,[23,24] no such association could be found. The crucial anticariogenic role of calcium was also evident in the present study, since the CCF children had a high salivary calcium concentration while other protective salivary parameters were similar to those of the CCA group.

The salivary MS concentration in FD was extremely low. There was also a tendency for lower MS in the CCF group compared with the CCA group. This is in line with previous studies showing a direct relationship between caries rate and MS levels.[23,25-27] The low MS levels in FD saliva may be associated with the high salivary flow rate rather than with the antibacterial activity of IgA and lysozyme, which were not increased in the FD group. The association between salivary flow rate and MS levels is in agreement with previous studies on children and young adults.[25,28]

The salivary lactobacilli level reflects the presence of bacteria harboring niches in the mouth, either iatrogenic or caused by carious cavities.[29] Since none of the children examined had niches secondary to orthodontic appliances or overhanging dental restorations, it was not surprising that the CCA group had the highest lactobacilli levels, due to carious cavities. Similarly to a previous report,[30] a dip-slide

tested lactobacilli level proved to be of paramount importance in the discrimination between children with and without caries.

Salivary buffering capacity in FD was comparable to that reported for 11- to 12-year-old Finnish children with low (0.63-0.70) DMFS levels,[28] but was slightly lower than that reported in another Finnish study.[31] Although buffering capacity was highest in CCA and lowest in FD, these differences did not reach statistical significance. This lack of significance may be due to the limited sensitivity of the methods used.

These simple, commercially available methods are widely used by many investigators to measure the buffering capacity and MS and lactobacilli levels in children.[26-28,30-33] They have been recommended by a working group from the Commission on Oral Health, Research, and Epidemiology (CORE).[5] The disadvantage of these methods is their semiquantitative nature, which limits the resolution power of statistical comparisons. Another contributing factor to the lack of significant differences in the results of buffering capacity was the difficulty in obtaining reliable amounts of stimulated whole saliva from children with FD, which may have interfered with the consistency of the values obtained.

Generally, the values for the various salivary components of the healthy control groups were similar to those previously reported in healthy chldren.[10,12,21,22,31,32,34-40] In addition, as previously shown,[31] the authors found a negative correlation between salivary flow rate and total protein content. Indeed, the FD group, while displaying the highest flow rate, had the lowest salivary total protein concentration. In contrast, the submandibular/sublingual protein concentration was found to be similar in FD and healthy control children.[4]

As stated in the Results section, several significant differences were found in regards to the concentrations of salivary components, but none concerning their output. The relevance of the concentrations' differences, as discussed in this section, will not be completely elucidated until confirmation or rejection of the present data regarding the output of salivary components will be obtained on a larger sample.

The role of IgA in oral immunologic defense against streptococcal infection has been considered part of the overall mucosal defense mechanism.[8,40,41] Minor salivary glands, which are responsible for the secretion of approximately 30-55% of IgA, react to antigenic challenges in the oral cavity by producing IgA.[40,42,43] The results of the present study may suggest that in FD, decreased IgA concentration reflects a reduced "need for protection," since the salivary infection level was low. An inverse relationship between caries experience and the concentration of IgA has been previously reported,[44] but the literature is inconsistent regarding the association between the caries rate and salivary IgA level.[28,45] The finding of a low IgA concentration with a normal output is in line with the above mentioned inconsistency.

The CCA group had the highest value of salivary lysozyme, which belongs to the nonimmunologic salivary defense system. This may suggest the presence of a feedback mechanism by which lysozyme is released into the oral cavity in response to the need of protection required against caries activity. However, in previous studies, no correlation was found between parotid and submandibular-sublingual whole salivary lysozyme concentrations and caries state.[28,34,46]

No statistically significant differences were found between the 3 groups for amylase concentrations. Similarly, Dodds et al,[47] reported no differences in total protein and amylase concentrations in parotid saliva between caries-free and caries-active adults. Although amylase may interact with oral bacteria to provide glucose from dietary starch, little is known about the significance of this interaction with plaque formation or dental caries.[48,49]

It is difficult to interpret the electrolyte values in the present study in view of lack of consensus as to their role in the caries process. While several investigators have reported higher potassium and chloride levels in parotid saliva from caries-active adults,[47,50] others ruled out an association between these electrolytes and the caries rate.[9,51] The authors' caries-active group had a significantly lower salivary concentration of potassium, while chloride was similar in both healthy control groups but lower among the FD children.

Salivary magnesium has been reported to be either unrelated[9,23,24,51] or directly associated with caries rate.[50] In the present study, magnesium was similar in both healthy control groups and significantly higher among the FD children.

Conclusions

1. The results of the study surmise an anticariogenic role of increased salivary flow rate in FD, that needs to be confirmed by a larger study.
2. The high salivary concentration of calcium in CCF children seems to be a significant anticariogenic factor.
3. Salivary levels of mutans streptococci and lactobacilli were associated with the salivary flow rate and possibly with the degree of caries activity (since the CCA group displayed the highest values of these parameters).
4. Investigation of the role of other salivary factors in the dental caries status of healthy and FD children should be continued in further studies.

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Abstract of the Scientific Literature

A Cephalometric Study of the Class II Correction Effects of the Eureka Spring

The Eureka Spring appliance (ES) is a Class II treatment alternative for noncompliant patients and, in Herbst tradition, has a compressible plunger assembly attached posteriorly to maxillary molars and anteriorly to the mandibular cuspid/bicuspid region. ES is reported to be advantageous over other Class II treatment modalities in noncompliant patients. The purpose of this study was to evaluate cephalometric treatment effects in such cases. Cephalometric measurements were obtained for 37 growing and nongrowing Class II patients at 2 time intervals, including insertion and removal of ES and analyzed using paired *t* tests ($P<.05$). Class I and favorable overjet and overbite relationships were obtained in all patients in a mean treatment time of 4.0±1.3 months. Significant changes attributed to the ES were dental and included changes in maxillary and mandibular molar and incisor position, angulations, and/or inclination and orientation of the occlusal plane to Frankfort Horizontal attributed to intrusion of teeth. No significant skeletal changes were established. Thus, the authors conclude that there may be specific advantages to ES over standard Class II correction methods.

Comments: Despite the absence of either a control or comparison group, this study demonstrates possible dental changes using ES with limited skeletal effects. **AW**

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