The Differential Diagnosis of Fluorosis

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Abstract

Following the introduction of the first fluorosis index by Dean, a series of fluorosis indexes were introduced. While they may differ in the specific way fluorosis is categorized, they all nevertheless use the same underlying diagnostic signs—originally described by Dean, Black, and McKay—that were causally linked to the development of enamel in areas with above-optimum fluoride in the drinking water. Underlying the various fluorosis indexes is the belief that specific clinical diagnostic criteria, based upon established clinical signs, can be utilized to differentiate fluorotic from nonfluorotic enamel opacities. These criteria repeatedly have been substantiated in studies in which the presence of enamel fluorosis, identified by clinical differential diagnosis, has been associated with fluoride exposure history. Further, to whatever extent nonfluorotic opacities have been misdiagnosed as fluorosis, observed estimates of association derived from analytical studies will have been underestimated. [J Public Health Dent 1999; 59(4):235-38]

Key Words: dental enamel, mottled enamel, diagnostic errors, fluorides, oral diagnosis.

Enamel fluorosis was first clinically described with scientific rigor by Black and McKay to identify what at that time could only be categorized manifestationally as mottled enamel (1,2). Following the identification of fluoride as the etiological cause of mottled enamel, Dean introduced the first enamel fluorosis index (3). Since that time, a series of fluorosis indexes have been introduced, and while they may differ in the specific way fluorosis is categorized, they all nevertheless use the same underlying diagnostic signs—originally described by Dean, Black, and McKay (1-3)—that were causally linked to the development of enamel fluorosis in areas with above-optimum fluoride in the drinking water (4). As several reviews of the relative merits of the various fluorosis indexes already exist (5-7), a re-review is neither necessary nor appropriate for this workshop. Rather, this paper will attempt to identify and discuss several issues related to the differential diagnosis of enamel fluorosis that bear directly on the attainment and interpretation of fluorosis risk factor data. These issues include: (1) the existing clinical criteria for the differential diagnosis of fluorotic versus nonfluorotic opacities; (2) the effect of misdiagnosis upon fluorosis prevalence studies and analytical epidemiologic studies; and (3) the effect in analytical studies of identifying subjects based upon fluorosis presence anywhere on the teeth, as compared to its presence on specific developmentally related enamel surfaces.

Clinical Criteria for Enamel Opacities

Underlying the various fluorosis indexes is the belief that specific clinical diagnostic criteria, based upon established clinical signs, can be utilized to differentiate fluorotic from nonfluorotic enamel opacities (8-11). In the milder forms of enamel fluorosis, signs can include narrow white lines following the perikymata, cuspal snowcapping, and a snowflaking appearance that lacks a clear border with unaffected enamel. As severity increases, confluent areas of opacity become more evident with more pronounced mottling, staining, and pitting, with marked anatomic defects visible in the most severe cases. These increasing levels of clinically observed fluorosis severity are closely associated with underlying histologic changes in hypomineralization (10). As shown in Table 1, accompanying clinical guidelines for the differential diagnosis of enamel fluorosis and nonfluorotic lesions also have been developed and in use for 30 years (12).

The premise that a presumptive diagnosis of enamel fluorosis can be made based solely upon clinical diagnostic criteria, in the absence of a definitive fluoride exposure history, has been challenged as inappropriate (13-16). However, the validity of differential criteria used to identify enamel fluorosis—criteria that originated based upon the clinical manifestations observed in areas with above-optimum fluoride concentrations in the drinking water—have been repeatedly substantiated in studies in which the presence of enamel fluorosis, identified by clinical differential diagnosis, has been associated with fluoride exposure history, unknown at the time of examination (17-20).

An illustration of this association can be drawn from a recent case-control investigation in which examinations were conducted by three calibrated examiners using the differential diagnostic criteria of Russell (12) to distinguish fluorotic from nonfluorotic opacities. Fluorosis examinations preceded the attainment of fluoride exposure histories by several months. Not surprisingly, this study found a strong association between mild-to-moderate enamel fluorosis and a history of fluoride supplementation during the first four to six years among lifelong residents of optimally fluoridated communities (21). Of interest to this discussion, however, was the observation that none of the subjects who were not diagnosed with fluorosis, but who were diagnosed as having two or more nonfluorotic

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TABLE 1
Clinical Criteria for Differential Diagnosis of Enamel Fluorosis [Adapted from Russell (12)]

Characteristic	Milder Forms of Enamel Fluorosis	Nonfluoride Enamel Opacities
Areas affected	Usually seen on or near tips of cusps or incisal edges.	Usually centered in smooth surface; may affect entire crown
Shape of lesion	Resembles line shading in pencil sketch; lines follow incremental lines in enamel, form irregular caps on cusps.	Often round or oval
Demarcation	Shades off imperceptibly into surrounding normal enamel.	Clearly differentiated from adjacent normal enamel
Color	Slightly more opaque than normal enamel; "paper white." Incisal edges, tips of cusps may have frosted appearance. Does not show stain at time of eruption (in milder degrees, rarely at any time).	Usually pigmented at time of eruption. Often creamy-yellow to dark reddish-orange
Teeth affected	Most frequent on teeth that calcify slowly (cuspids, bicuspids, second and third molars). Rare on lower incisors. Usually seen on six or eight homologous teeth. Extremely rare in deciduous teeth.	Any tooth may be affected. Frequent on labial surfaces lower incisors. May occur singly. Usually one to three teeth affected. Common in deciduous teeth
Gross hypoplasia	None. Pitting of enamel does not occur in the milder forms. Enamel surface has glazed appearance, is smooth to point of explorer	Absent to severe. Enamel surface may seem etched, be rough to explorer detection
Detection	Often invisible under strong light; most easily detected by line of sight tangential to tooth crown surface.	Seen most easily under strong light on line of sight perpendicular to tooth

opacities (n=31), had a history of this inappropriate supplementation. A similar lack of association was seen with the other important fluoride exposures in that study.

Potential Effects of Misdiagnosis

Even though the clinical criteria appear valid, it is important to consider what the potential effects of misdiagnosis of fluorotic and nonfluorotic opacities are, especially as they bear upon fluorosis risk factor identification. Figure 1 shows the possible outcomes of a diagnosis of a subject for enamel fluorosis. Subjects clinically diagnosed as having enamel fluorosis can either truly have enamel fluorosis or have been misdiagnosed (i.e., are false positives). At the same time, subjects who are diagnosed as having nonfluorotic opacities either can be truly fluorosis free or again have been misdiagnosed (i.e., are false negatives). The effect of this misdiagnosis or nondifferential misclassification of subjects will differ between prevalence surveys and analytical risk factor studies.

The effects of misdiagnosis upon a prevalence survey are intuitive. A misdiagnosis of nonfluorotic opacities as enamel fluorosis—that is, generating false positives—will inflate the fluorosis prevalence value, while misdiagnosing fluorotic opacities as nonfluorotic—that is, generating false negatives—will have the opposite effect, deflating the prevalence value.

FIGURE 1
Possible Outcomes of Fluorosis Diagnosis

	True Nature of Opacities	
Clinical Diagnosis	Enamel Fluorosis	Nonfluorotic Enamel Opacities
Enamel Fluorosis	True Cases	False Positives
Nonfluorotic Enamel Opacities	False Negatives	True Noncases

In contrast to the prevalence study, in an analytical study (i.e., a case-control or cohort study), any effect of this nondifferential misclassification of subjects, which mixes true cases with noncases, would be to mask or diminish obtained measures of association (i.e., risk ratio or odds ratio) (22). Figure 2a shows an illustrative example in which true exposure frequencies in a fictitious population are 80 percent for cases and 40 percent for controls, yielding a true odds ratio of 6. Figure 2b shows the effect of a misdiagnosis rate of 50 percent. While the numbers of cases and controls as well as the number of exposed and unexposed have remained the same, the misdiagnoses has acted to mix true cases with controls and vice versa, yielding equal exposure frequencies between groups and a resultant odds ratio of unity. While this example clearly represents

FIGURE 2a
True Exposure Frequencies and Resultant Odds Ratio in a Fictitious Population

	Case	Controls	
Exposed	80	40	120
Unexposed	20	60	80
	100	100	

True odds ratio=(80)(60)/(20)(40)=6.

FIGURE 2b
Effect of 50 Percent Misdiagnosis upon Exposure Frequency Estimates and Resultant Odds Ratio Estimate in a Fictitious Population

	Case	Controls	
Exposed	60	60	120
Unexposed	40	40	80
	100	100	

Observed odds ratio=(60)(40)/(40)(60)=1.

an extreme case of misdiagnosis, it demonstrates that to whatever extent this misclassification occurs, the resultant measure of association will be reduced or masked entirely. Therefore, because observed risk factor associations have only the potential to increase, were all misdiagnoses eliminated, the currently observed associations between supplements, for example, and fluorosis cannot be dismissed as potentially due to clinical diagnostic errors.

A related question is whether a fluoride exposure, such as fluoride supplementation, could be associated mistakenly, through the effect of a confounding variable, with nonfluoride opacities misdiagnosed as enamel fluorosis. Figure 3 diagrammatically demonstrates the theoretical situation under which an observed strong association between a fluoride exposure and mottled enamel, misdiagnosed as enamel fluorosis, could be due to some other confounding factor. Figure 3a shows an apparent strong association that is observed between a fluoride exposure (F) and mottled enamel (M). As shown in Figure 3b, for this apparent association to be spurious, there must be a second, confounding exposure (C) that is strongly associated both with the mottled enamel and noncausally with the fluorosis exposure (23). An association may or may not exist between the fluoride exposure and mottled enamel in this confounding situation.

Thus, an observed strong association between a fluoride exposure and mottled enamel could only be due to misdiagnosis in the situation where there was some other unidentified exposure, unadjusted for in the analysis, that was strongly associated both with exposure to the suspected risk factor and with the enamel opacities. This improbable situation is theoretically akin to the more common occurrence of one fluoride exposure confounding another fluoride exposure's association with enamel fluorosis, a situation protected against by adequate exposure history and multivariate analytical techniques. Thus, in fluorosis risk analyses, to be able to dismiss an observed association as being spuriously based upon misdiagnosis or misclassification, it would be necessary to specifically identify the presence of an uncontrolled confounder for which, to date, there is no evidence.

Potential Effects of Person vs Developmental Site Diagnosis

The identification in descriptive studies of individuals with fluorosis based upon its presence anywhere throughout the dentition provides for a valid overall estimate of fluorosis prevalence, with the description of patterns of distribution across the dentition providing further insights into possible etiology and esthetic consequences. However, as has been illustrated previously in the literature, in the analytical investigation of the risk associated with time-related fluoride exposures, the identification of fluorosis cases based nondifferentially upon fluorosis anywhere in the mouth may act to mask true underlying risk associations (24). Table 2 illustrates this effect, showing how the association between supplement use during the third through sixth years with enamel fluorosis on early forming enamel (representing the esthetically important anterior teeth) would be masked by the use of a whole-mouth fluorosis determination (e.g., Dean's index). However, the point of emphasis here is that while this potential for nondifferential misclassification bias can mask an association, it cannot act to spuriously create the appearance of an association (22). Therefore, observed associations between fluoride exposures and fluorosis cannot be dismissed as spurious due to the use of whole-mouth-derived fluorosis identification, but rather must be viewed as minimum estimates.

FIGURE 3a
Apparent Strong Association Between Fluoride Exposure (F) and Mottled Enamel (M)

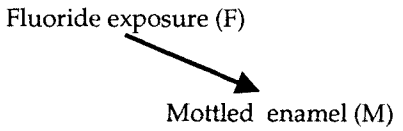

FIGURE 3b
Apparent Strong Association Between Fluoride Exposure (F) and Mottled Enamel (M) Explained by Presence of a Confounding Exposure (C) [Adapted from Schlesselman (23)]

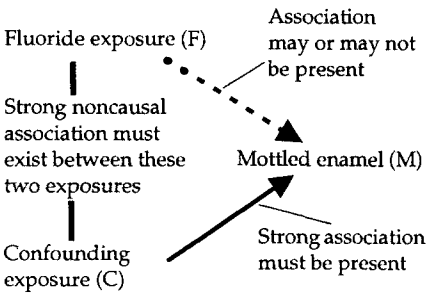

TABLE 2
Illustration from Case-control Investigation of 11–14-year-old Nonfluoridated Massachusetts and Connecticut Children, of the Masking of an Association Between Enamel Fluorosis and a Time-related Fluoride Exposure that Can Occur by Identifying Fluorosis Cases Based on Presence of Fluorosis Anywhere in Mouth [Adapted from Pendrys (24)]

Fluoride Suppl. Use	Enamel that Began to Form During: Year 1	Year 3	Dean's Index
None*	1.0	1.0	1.0
Yrs 3–6	3.3† (1.5, 7.5)	2.1 (0.9, 5.0)	2.0 (0.7, 5.8)

*Exposure reference group.
†Mantel-Haenszel odds ratios and 99 percent confidence intervals are adjusted for supplementation during year 1 and median household income.

Finally, it is important in analytical studies for the fluorosis case definition to include a clear fluorosis severity threshold because (1) the association between a particular fluoride exposure and enamel fluorosis may vary depending upon the chosen threshold of fluorosis severity, (2) the esthetic consequences are clearly related, and (3) it is likely that differential diagnostic decisions become more difficult as the severity of fluorosis being diagnosed approaches normality. For example, data drawn from the same case-control study referred to above (21) showed that the proportion of subjects diagnosed with nonfluorotic opacities was about double for the questionable group as compared to the case or control groups in that study.

In summary, existing evidence supports the validity of differential clinical diagnosis of enamel fluorosis when appropriate criteria are employed. Further, this paper has attempted to demonstrate that the effect of fluorosis misdiagnosis upon risk factor assessment, to whatever degree it might occur, will be to mask or diminish the observed estimates of association between enamel fluorosis and the fluoride exposure being studied.

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