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Reassessment of Oral Frenula in Ehlers–Danlos Syndrome: A Study of 32 Patients With the Hypermobility Type

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TO THE EDITOR:

Ehlers–Danlos syndrome (EDS) comprises a group of heritable connective tissue disorders characterized by joint hypermobility and skin, vascular, and soft tissue fragility. Among them, the hypermobility type (EDS-HT), which is now considered indistinguishable from the joint hypermobility syndrome (JHS) [Tinkle et al., 2009], is likely the most common variant with a presumed population prevalence of ~1% [Hakim and Sahota, 2006]. It remains a largely underrecognized, and, consequently, untreated condition. In order to help practitioners in dealing with JHS/EDS-HT, specific diagnostic criteria were established [Grahame et al., 2000], but the need of revising them is pressing [Remvig et al., 2011].

De Felice et al. [2001] indicated the absence of lingual/lower labial frenula as a possible sign in JHS/EDS-HT and EDS classic type (EDS-CT). Subsequent observations on EDS-HT/EDS-CT patients and subjects with unspecified EDS failed to confirm this suggestion [Böhm et al., 2001; Shankar et al., 2006]. However, the debate persists with research groups still proposing the absence of oral frenula as a possible diagnostic sign in various forms of EDS [Perrinaud et al., 2007; Machet et al., 2010]. We evaluated 32 patients with JHS/EDS-HT in order to estimate the rate and possible presentation of oral frenulum involvement in this EDS subtype (Fig. 1).

Subjects were selected from some 100 index patients with various forms of EDS attending our multidisciplinary joint hypermobility clinic. Selection was based on the patient's availability to undergo further intraoral studies. Diagnosis of JHS/EDS-HT was assessed on the basis of published diagnostic criteria for JHS [Brighton criteria; Grahame et al., 2000] and EDS-HT [Villefranche criteria; Beighton et al., 1998]. In our clinical practice, the Brighton criteria are the most stringent for young–adult, adult and older patients, while the Villefranche criteria are the best for individuals in the pediatric age. Patients were included if they met at least either one of these two sets of criteria. Both sets comprise generalized joint hypermobility as a major manifestation. Accordingly, generalized joint hypermobility was assessed applying the Beighton score [Beighton et al., 1973] and considered present with a score of 4/9 for the Brighton criteria and 5/9 for the Villefranche criteria. Further maneuvers were also applied in order to estimate joint mobility outside the joints evaluated for Beighton score calculation. Skin/superficial connective tissue aspects were assessed qualitatively on the basis of accumulated experience. Additional findings, actually not incorporated in either set of criteria, were also registered. Other heritable connective tissue disorders were excluded clinically. Individuals with a doubtful or incomplete diagnosis were also excluded.

Twenty-nine were females (90.6%) and 3 males (9.4%) [mean age (SD) = 31.1 (12.4)]. Main manifestations were summarized in Table I. According to previous studies qualitatively investigating the rate of inferior labial and lingual frenula hypoplasia in EDS [Böhm et al., 2001; De Felice et al., 2001; Shankar et al., 2006;

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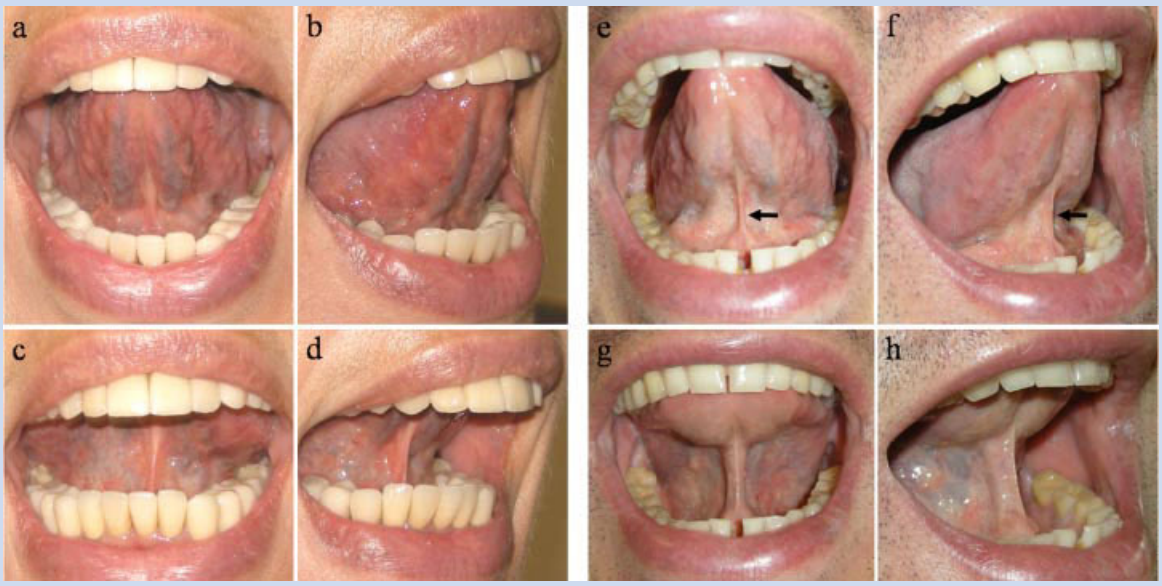

FIG. 1. Comparison between a typical JHS/EDS-HT patient with hypoplasia of the lingual frenulum (female; a–d) and a normal control (male; e–h). In the JHS/EDS-HT patient, note the apparent absence of the lingual frenulum with the tip of the tongue touching the incisal papilla on frontal (a) and lateral (b) views [method (a)]. Conversely, in the same subject, the lingual frenulum is visible, though hypoplastic after asking to suck up the tongue and maintain it against the hard palate on frontal (c) and lateral (d) views [method (b)]. In the control subject the lingual frenulum is clearly visible by both methods [panels e and f for method (a), and panels g and h for method (b)]. For method (a), the lingual frenulum is indicated by an arrow in the control person.

TABLE I. Summary of the Main Manifestations in the Patient' Group

Manifestation	Total	%
Congenital joint hypermobility	23/32	71.8
Clumsiness in infancy	16/32	50
Beighton score ≥ 4	29/32	90.6
Chronic/recurrent (>3 months) arthralgias	32/32	100
Back pain	27/32	84.3
Chronic/recurrent myalgias	27/32	84.3
Recurrent sprains/strains	22/32	68.7
Recurrent dislocations	23/32	71.8
Recurrent (>3) soft tissue lesions	16/32	50
Chronic fatigue	28/32	87.5
Soft/velvety skin	25/32	78.1
Hyperextensible skin	9/32	28.1
Easy bruising	25/32	78.1
Eyelid ptosis/myopia	16/32	50
Varicose veins	5/32	15.6
Abdominal hernias	1/32	3.1
Vescical/uterine/rectal prolapse	4/32	12.5
Limb paresthesias	23/32	71.8
Recurrent tachycardias	22/32	68.7
Gastrointestinal complaints	25/32	78.1

Perrinaud et al., 2007; Machet et al., 2010], we first attempted to replicate this observation requesting patients to stretch the lower lip and to touch the incisal papilla with the tip of tongue [method (a)]. Afterwards, we asked the patients to confirm the results obtained with method (a) by sucking up the tongue and maintaining it against the hard palate [method (b); Marchesan, 2005]. This further procedure, originally used for a quantitative/semi-quantitative evaluation of the lingual frenulum length in a Speech clinic, was selected in order to grossly evaluate a functional contribution to the apparent absence/hypoplasia of the lingual frenulum reported with method (a). Data were compared with a group of 64 controls [mean age (SD): 31.6 (12.15); $P = 0.919$]. Controls were selected from healthy subjects attending genetics clinic as definitely unaffected relatives of index patients without inherited connective tissue disorders, and were matched for sex, age, and ethnic origin with the patients' group.

We failed to detect complete absence of the lower labial frenulum in any patient and control subject. Mild hypoplasia of this frenulum cannot be excluded, but we did not find any reproducible method to test this hypothesis. Lack of visualization of the lingual frenulum was reported in 23 patients and 13 control by method (a) ($P < 0.0001$; sensibility 71.9%; specificity 79.7%; positive predictive value 63.9%; negative predictive value 85%), and in 4 patients and 1 control person by method (b) ($P = 0.023$; sensibility 12.5%; specificity 98.4%; positive predictive value 80%; negative predictive value 69.2%).

Identifying sufficiently specific clinical signs is an essential step for developing stringent diagnostic criteria for (heritable) conditions lacking a consistent confirmatory molecular test. This is the case for JHS/EDS-HT. Assessment of oral frenula is a historically valid method for studying various genetic conditions [Mintz et al., 2005]. Actual knowledge of the role of oral frenula in clinically assessing EDS is confused by various bias, including clinical variability in the published papers, lack of a control group in one study [Böhm et al., 2001], and indirect patients' evaluation by using a self-administrated questionnaire in another [Shankar et al., 2006]. Therefore, although an increased rate of oral frenula hypo/aplasia in EDS is likely, the true nature and consequently the cause of this finding in this condition remain obscure.

We confirmed that the clinical absence/aplasia of the lingual frenulum is statistically more common in JHS/EDS-HT patients compared to controls. However, in line with previous studies, the absence/presence of this sign shows low specificity and relatively low positive predictive value by applying method (a). After asking to perform a more complex task [i.e., method (b)], many patients and fewer controls with apparent lack of the lingual frenulum by method (a) demonstrated the persistence of this anatomic component, which appeared somewhat hypoplastic. This reduction in rate of absence of the lingual frenulum was significantly more evident among patients. This finding is difficult to explain. However, a possible mechanism can be an impaired muscle coordination in complex functions, such as mouth opening and tongue movements, which may mirror the well-known lack of proprioception observed in the lower limbs [Sahin et al., 2008] and cause an overestimation of the absence of the lingual frenulum by method (a) in JHS/EDS-HT. The lingual frenulum is a mucosal attachment with the primary function of providing stability for the tongue [Mintz et al., 2005]. The tongue is a highly mobile structure with complex functions composed of 8 muscles: 4 extrinsic muscles acting to change the position of the tongue and anchoring it to specific bones, and 4 intrinsic muscles modifying the shape of the tongue and lacking any bone anchorage. Therefore, as most EDS patients present a combination of myofascial pain, internal joint derangement and arthralgia at one or both the temporomandibular joints [De Coster et al., 2005] whose activities are interrelated with those of the tongue, it is possible that, in JHS/EDS-HT, tongue incoordination may be facilitated by an underlying temporomondibular joint dysfunction. This is partly supported by the difficulties that we noted in performing method (b) among patients compared to controls. In fact, many patients required repeated attempts before successfully adhering their tongue to the hard palate.

In conclusion, absence/aplasia/hypoplasia of the oral frenula and, in particular, the lingual frenulum may help diagnosis establishment of JHS/EDS-HT in specific cases. In order to add specificity to this investigation, complete adherence of the tongue body to the hard palate should be elicited. Further studies are needed before including this sign among the JHS/EDS-HT diagnostic criteria.

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