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ORIGINAL ARTICLE

Auriculotemporal Frey syndrome not associated with surgery or diabetes: systematic review

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Abstract

Patients who undergo salivary gland, neck, or facelift surgery or suffer from diabetes mellitus often develop Frey syndrome (also known as auriculotemporal syndrome or gustatory sweating). Frey syndrome has been occasionally reported to occur in subjects without history of surgery or diabetes but this variant of Frey syndrome has not been systematically investigated. We searched for original articles of Frey syndrome unrelated to surgery or diabetes without date and language restriction. Article selection and data extraction were performed in duplicate. Our systematic review included 76 reports describing 121 individual cases (67 males and 54 females) of Frey syndrome not associated with surgery or diabetes. The age at onset of symptoms was ≤ 18 years in 113 (93%) cases. The time to diagnosis was 12 months or more in 55 (45%) cases. On the other hand, an allergy evaluation was performed in half of the cases. A possible cause for Frey syndrome was detected in 85 (70%) cases, most frequently history of forceps birth ($N = 63$; 52%). The majority of the remaining 22 cases occurred after a blunt face trauma, following an auriculotemporal nerve neuritis or in association with a neurocutaneous syndrome. The cause underlying Frey syndrome was unknown in 36 cases.

Conclusion: Frey syndrome not associated with surgery or diabetes almost exclusively affects subjects in pediatric age and is uncommon and underrecognized. Most cases occur after forceps birth. There is a need to expand awareness of this pseudo-allergic reaction among pediatricians and allergists.

What is Known:
- *Pre-auricular reddening, sweating, and warmth in response to mastication or a salivary stimulus characterize Frey syndrome.*
- *It usually occurs after salivary gland surgery and in diabetes.*

What is New:
- *In children, Frey syndrome is rare, and most cases occur after a forceps-assisted birth.*
- *In childhood, this condition is often erroneously attributed to food allergy.*

Keywords Auriculotemporal syndrome · Forceps birth · Frey syndrome · Gustatory sweating · Pseudo-allergic reaction

Introduction

Mastication or a salivary stimulus may be followed by rapid reddening of the pre-auricular region, normally associated with local warmth, sweating, and general discomfort, and occasionally also with shedding of tears or watery otorrhea [1]. This phenomenon was first described by M. Duphenix in 1757 and subsequently by J. Baillarger in 1853 [2, 3]. However, the better characterization was made in 1923 by the Polish Jewish neurologist Łucja Frey-Gottesman (1889–1942). The condition is nowadays referred to as auriculotemporal (nerve) syndrome, gustatory sweating, or Frey syndrome [2, 3]. It typically and rather commonly occurs 6 to 18 months after salivary gland, neck, or facelift surgery [1], and in diabetes mellitus [4].

The aims of this systematic review of the literature were to document demographics, presentation, diagnostic difficulties, and causes of Frey syndrome not associated with surgery or diabetes.

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Methods

Literature search strategy

The PRISMA recommendations for reporting systematic reviews were used. The literature search was conducted in the databases Excerpta Medica, National Library of Medicine, and Web of Science up to July 2021 without date and language restriction. Search terms were "auriculotemporal syndrome", "gustatory sweating", or "Frey syndrome". References listed within bibliographies of the retrieved records and reports already known to the authors were also considered for inclusion.

The literature search was conducted by two investigators, who independently screened titles and abstracts of all reports in a non-blinded fashion to remove irrelevant reports. Discrepancies in study identification were adjudicated by a senior investigator. Subsequently, full-text publications were reviewed to decide whether the report fitted the eligibility criteria of the review.

Selection criteria—data extraction

Original articles reporting individual cases of Frey syndrome not associated with surgery or diabetes were considered. Only patients with episodes of (a) acute onset of reddening of the pre-auricular region (with or without local warmth, general discomfort, sweating, shedding of tears, or watery otorrhea), (b) beginning within a few seconds after onset of eating (or even immediately before eating), and (c) resolving within minutes after termination were included. The history and the examination of each case were carefully addressed with respect to laterality, age at symptoms onset, time interval from symptoms onset to diagnosis, past medical history including forceps-assisted vaginal birth [5], face trauma, coexisting conditions, or evaluation by an allergic disease specialist (with or without testing for immediate-type hypersensitivity). The occurrence of a positive family history, defined as at least two first-degree family members with Frey syndrome not associated with surgery or diabetes, was also addressed. If needed, attempts were made to contact original authors to obtain missing information.

Completeness of reporting—analysis

Completeness of reporting was judged for each included case using the following three components [6]: (1) detailed description of history, symptoms, and findings; (2) information on diagnostic workup, and (3) management and follow-up. Each component was rated as 1, 2, or 3 and the reporting quality was graded according to the sum of each item as excellent (7 to 9), good (4 to 6), or acceptable (≤ 3).

Categorical data are presented as counts and were analyzed using the Fisher exact test [7]. Continuous data are shown as medians and interquartile ranges and were compared using the Kruskal–Wallis test with the post hoc Dunn comparison [7]. Statistical significance was defined by two-sided P-values of < 0.05.

Results

Search results—reporting completeness

The literature search returned 1191 potentially relevant reports (Fig. 1). After removing irrelevant reports, 109 full-text publications were reviewed for eligibility. For the final analysis, we retained 76 reports describing 121 individual cases of Frey syndrome not associated with surgery or diabetes [5, 8–82]. The mentioned reports were published since 1945 in English ($N=54$), Spanish ($N=20$), and French ($N=2$) from the following countries: Spain ($N=23$), the USA ($N=15$), the UK ($N=13$), France ($N=3$), Canada ($N=3$), Turkey ($N=3$), Brazil ($N=2$), Germany ($N=2$), Israel ($N=2$), Australia ($N=1$), Austria ($N=1$), Belgium ($N=1$), Colombia ($N=1$), Denmark ($N=1$), Dubai ($N=1$), India ($N=1$), Ireland ($N=1$), Italy ($N=1$), and South Africa ($N=1$). Reporting comprehensiveness was excellent in 21, good in 92, and acceptable in the remaining 8 cases.

Search results

Presentation

In the 121 cases, age at onset of symptoms was ≤ 18 years in 113 cases (93%). A reddening of the pre-auricular region was observed in all cases. Sweating, local warmth, and general discomfort were reported only in a minority of cases and were significantly less common among pediatric cases (Table 1). Shedding of tears or watery otorrhea was never noted. Wheals, itching, scratch marks, and symptoms or signs consistent with a multisystem involvement were also never reported.

Frey syndrome was unilateral in 100 (83%) cases (right-sided more frequently than left-sided) and bilateral in the remaining 21 (17%) cases (Table 2). The time to diagnosis was ≥ 12 months in 55 (45%) cases. On the other hand, an allergy evaluation was performed in half of the cases. A possible cause for Frey syndrome was detected in 85 (70%) cases, most frequently history [9, 10, 12, 14, 15, 18, 20, 22, 23, 26, 28, 30–34, 36, 38, 41, 42, 49, 50, 54, 57, 58, 62, 63, 66–68, 71, 79, 82, 83] of forceps-assisted birth ($N=63$; 52%). The majority of the remaining 22 cases occurred after a blunt face trauma, following an auriculotemporal nerve neuritis or in association with a

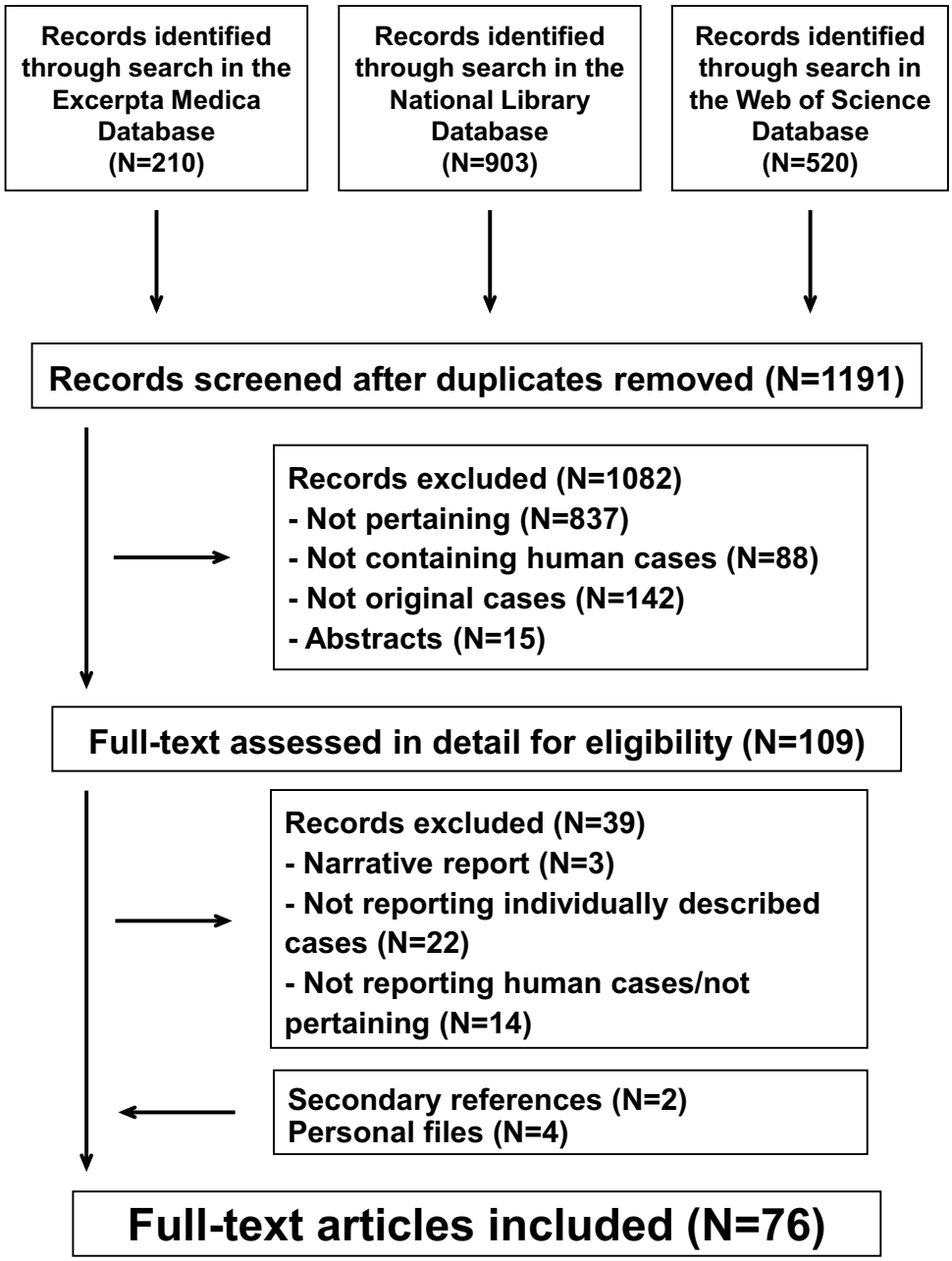

Fig. 1 Auriculotemporal Frey syndrome not associated with surgery or diabetes mellitus. Flowchart of the literature search process

Table 1 Symptoms and signs other than local reddening in 121 cases of auriculotemporal Frey syndrome without history of salivary gland, neck, or facelift surgery

	All	Children	Adults	*P*-value
N	121	113	8	
Sweating, *N*	14	6	8	< 0.01
Local warmth, *N*	13	6	7	< 0.01
General discomfort, *N*	6	0	6	< 0.01
Shedding of tears, *N*	0	0	0	
Watery otorrhea, *N*	0	0	0	

neurocutaneous syndrome (Table 3) and were significantly older ($P < 0.05$) than the other cases. The cause underlying Frey syndrome was unknown in the remaining 36 cases. Interestingly, Frey syndrome was bilateral in 15 (41%) of the latter 36 cases ($P < 0.0001$ versus remaining cases). Furthermore, the cases noted after forceps birth were more frequently male ($P < 0.05$ versus non-forceps cases).

Management—course

Reassurance about the benign and non-allergic nature of symptoms and signs was the most frequently recommended treatment. One adult case [77] was injected

Table 2 Characteristics of 121 patients 0.15 to 79 years of age affected by auriculotemporal Frey syndrome without history of salivary gland, neck, or facelift surgery. Date are presented either as frequency or as median and interquartile range

	All	Cause found		Unknown causes◆
		Forceps birth	Further causes	
N	121	63	22	36
Males to Females	67:54	41:22✙	11:11	16:20
Age at onset of symptoms				
Years	0.6 [0.4–1.0]	0.5 [0.4–0.6]	5.8● [1.3–18]	0.5 [0.4–1.2]
≤ 18 years, *N*	113	63	16	34
Time to diagnosis				
Months	7.2 [1.2–24]	7.2 [1.2–36]	6.0 [0.0–16]	3.6 [0.0–17]
≥ 12 months, *N*	55	30	12	13
Familiarity, *N*	7	3	0	4
Laterality				
Unilateral	100	59	20	21
Right	56	36	12	8
Left	38	19	8	11
Unspecified	6	4	0	2
Bilateral	21	4	2	15×
Allergy investigation	60	40	4	16
Without testing	25	16	8	1
With testing	35	24	3	8

◆Delivery was explicitly non-forceps-assisted in 31 of the 36 cases (no corresponding information was available for the remaining cases). ✙$P < 0.05$ versus non-forceps. ●$P < 0.05$ versus forceps birth and unknown causes. ×$P < 0.0001$ versus further cases and forceps-assisted birth

intradermally botulinum toxin (but the effect on the symptoms was poorly documented).

The follow-up was documented in 37 cases: (a) all symptoms and signs disappeared within 2 months to 5 years in 14 cases; (b) symptoms and signs ameliorated within 5 weeks to 2½ years in 13 cases; (c) symptoms and signs were unaltered after a follow-up of 4 months to 6 years in the remaining 10 cases.

Discussion

Frey syndrome mainly results from an aberrant innervation of the auriculotemporal branch of the mandibular nerve following surgery in the proximity of the parotid gland or in the context of diabetes [1, 4]. The present literature review on auriculotemporal Frey syndrome not associated with surgery

Table 3 Causes other than forceps-assisted delivery in 22 subjects (11 males and 11 females) with Frey syndrome without history of surgery

Cause	No	Age at symptoms onset (years)	References
Blunt face trauma			
With mandibular condyle facture	8	2.1, 13, 17, 22, 23, 26, 28, adulthood	[11, 13, 21, 25, 52, 55, 61, 75]
Without mandibular condyle fracture	1	0.4	[14]
Congenital neurocutaneous syndrome			
Neurofibromatosis type 1	4	0.4, 0.8, 1.2, 5.8	[51, 53, 80]
PHACE syndrome	1	0.1	[81]
Auriculotemporal nerve neuritis			
Herpes simplex virus	2	6.0, 20	[29, 74]
Varicella zoster virus	2	1.2, 6.5	[64, 76]
Further causes			
Trifid mandibular condyle	1	Childhood	[60]
Facial burns	1	Childhood	[77]
Parotid hemangiopericytoma	1	1.3	[47]
Moebius syndrome	1	0.7	[73]

Table 4 Differential diagnosis between auriculotemporal Frey syndrome and immediate type food allergy in infancy and childhood

	Auriculotemporal Frey syndrome	Immediate type food allergy
Cause	Aberrant innervation of the auriculotemporal nerve	Immune mediated
Culprit food	Any food	Specific food*
Time latency from food intake	≤ 30 s (at times before mastication)	Immediate (occasionally 1–2 h)
Skin involvement		
Localization	Pre-auricular region, mostly unilateral	Any skin area including mucosae
Findings	Erythema, warmth, and occasionally sweating	Urticaria, angioedema
Multisystem involvement	None	Respiratory, cardiovascular, gastrointestinal

*Most cases (≥ 90%) are triggered by cow's milk, hen's egg, soy, wheat, fish, tree nuts, seeds, peanuts, and shellfish

or diabetes may be essentially recapitulated and discussed in four points.

First, most case cases are unilateral and occur in pediatric age.

Second, three very typical features of Frey syndrome [1], that is, sweating, local warmth, and general discomfort, are relatively uncommon in subjects ≤ 18 years of age.

Third, various causes may underlie this form of Frey syndrome including blunt face trauma, neuritis, and a neurocutaneous syndrome. However, every second case occurs in children with history of forceps birth. Hence, it is assumed that forceps birth occasionally results in Frey syndrome [83]. Finally, no apparent cause was found in about one-third of cases. Many cases of Frey syndrome of unknown causes were bilateral or familial. It is therefore tempting to assume that prenatal factors account for some of the latter cases (the term idiopathic has also been suggested to denote these cases).

Fourth, the diagnosis of Frey syndrome not associated with surgery or diabetes may be tricky, the time to diagnosis is often ≥ 12 months and an allergy evaluation is performed in every second case. In our opinion, in Frey syndrome, many points should divert from suspecting food allergy as the cause, including the reddening occurring in the absence of pruritus, angioedema, signs consistent with a multisystem involvement, the quick spontaneous disappearance, and the occurrence on challenge with a variety of foods, as shown in Table 4 [84].

The results of this systematic review, which included 121 cases, are in line with those of a French multicenter inquiry among pediatricians and allergists that disclosed 48 Frey syndrome cases [85].

Reassurance represents in our opinion the mainstay of management in Frey syndrome not associated with surgery or diabetes [86, 87]. In addition to obtaining a detailed history and examination, reassurance therapy consists of making the diagnosis, explaining the pathophysiology of signs and symptoms, emphasizing that there is nothing to worry about, suggesting that signs and symptoms often ameliorate or resolve with time, discouraging further investigations, eliminating diets or restrictions, and recommending regular follow-up appointments [86, 87]. Intradermic botulinum toxin has been shown to reduce excessive sweating in post-surgical Frey syndrome [1]. Available data do not support the prescription of this treatment option in children with Frey syndrome, mainly because sweating is rare in these cases.

The most important limitation of this review arises from the small number of published reports on Frey syndrome not associated with surgery or diabetes. Furthermore, completeness in reporting cases was often rather low.

Conclusions

Frey syndrome not associated with surgery or diabetes almost exclusively affects subjects in pediatric age, and is uncommon and underrecognized. Forceps birth is the most frequent cause. The initial diagnosis may be established based on history and physical examination alone. There is a need to expand awareness of this pseudo-allergic reaction among pediatricians and allergists to avoid redundant investigations, unnecessary management, and apprehension.

Authors' contributions CB, GPM, MGB, and MMB conceptualized and designed the study, contributed to data interpretation, drafted the initial manuscript, and revised the manuscript. CB and MMB undertook, supervised by SAGL, the literature search and analyzed the data. GPR and BGS critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted.

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Declarations

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Conflict of interest The authors declare no competing interests.

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