



## Frey Syndrome

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**Objective** To describe the features of Frey syndrome (auriculotemporal nerve dysfunction with gustatory flushing) in childhood.

**Study design** A multicenter, retrospective, descriptive observational national case series study was conducted with the help of French academic societies. Diagnostic criteria were based on clinical history, and sometimes also on photographs or provocation tests.

**Results** Forty-eight cases were identified, with 2 subtypes: 35 unilateral and 13 bilateral. Associated sweating was reported in only 10% of cases. Diagnosis was made in only 20% of children at the first consultation and inappropriate dietary restriction was prescribed for 21%. Instrumented vaginal delivery was significantly associated with unilateral forms (OR [unilateral vs bilateral] = 29; 95% CI 3.99-311.58;  $P < .001$ ). The outcome was favorable overall with 57% regression, 20% recovery, and only 23% persistence of initial symptoms. Regression was more frequent in unilateral forms (OR = 6.60; 95% CI 1.23-44.04;  $P = .016$ ), observed in 69% of unilateral forms at a median age of 27 (24-48) months. Recovery predominated in bilateral forms (OR = 0.05; 95% CI 0-0.38;  $P = .001$ ), observed in 58% of bilateral cases at a median age of 8 (7-9) months.

**Conclusions** Frey syndrome in childhood is a rare but benign condition with mild symptoms and a favorable outcome in most cases. Unilateral forms are mostly associated with instrumented delivery. Pediatricians should be familiar with this disorder in order to avoid misdiagnosis, mainly as food allergy, and unnecessary referrals and tests. (*J Pediatr* 2016;174:211-7).

**F**rey syndrome is an auriculotemporal nerve dysfunction characterized by transient flushing and warmth, and sometimes sweating of the face in the territory of auriculotemporal nerve. The nerve is a branch of the mandibular nerve of the trigeminal nerve complex. Symptoms occur during meals a few seconds after eating, last for a few minutes, and occur particularly with acidic, spicy, and sour foods.<sup>1</sup>

Frey syndrome was first described by Kastremysky in 1740, and by Duphenix in 1757.<sup>2</sup> In 1923, Lucja Frey, a Polish neurologist, identified the role of the auriculotemporal nerve in this disorder.<sup>3</sup> The pathophysiology is incompletely understood. The prevailing hypothesis is that local trauma on the auriculotemporal nerve leads to damaged autonomic fibers and aberrant regeneration. Among adults, the disorder often is secondary to a traumatic or surgical lesion in the region of the parotid gland region, with symptoms appearing a few weeks, months, or years after the initial trauma. Frey syndrome is much less common in children, occurring mainly during early infancy, with no history of surgery or obvious postnatal trauma; 92 pediatric cases are listed in the PubMed database between 1948 and 2015, 72 of which had no history of local surgery, postnatal trauma, tumor, or malformation context. The largest series to date collected 9 cases without follow-up data.<sup>4</sup> Diagnosis was more difficult than for adult cases and was often made, after extensive medical evaluation, by pediatric allergists. Food allergy was the main differential diagnosis<sup>5</sup> because of its increasing prevalence and similar clinical presentation (rash after ingestion), especially in bilateral cases.<sup>4</sup>

In this context, we conducted a national study with the aim to describe the specific clinical features, evolution, and management of pediatric Frey syndrome occurring in the absence of surgery, obvious postnatal trauma, malformation, or tumor context. We also compared unilateral and bilateral forms.

### Methods

A multicenter, retrospective, observational national case series study was performed from September 2014 to June 2015. Because Frey syndrome is linked to nerve dysfunction, but has only skin manifestations mimicking allergy, it can be diagnosed and managed in the primary, secondary, or tertiary care setting by various types of physician (pediatricians, allergists, otolaryngologists, or dermatologists). Pediatric tertiary care centers and members of French pediatric/allergy/dermatology/otolaryngology academic societies were initially contacted by

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e-mail. Inclusion criteria were Frey syndrome in patients under 18 years old (excluding surgical or postnatal trauma, malformation, and tumor settings) with diagnosis based on clinical history (transient flushing and warmth, and sometimes sweating of the face in the territory of the auriculotemporal nerve occurring during meals a few seconds after eating, lasting for a few minutes, and occurring particularly with acidic, spicy, and sour foods), and in some cases also photographs or provocation test.

A provocation test was an open challenge with food eliciting the most symptoms according to the parents, performed during the medical consultation; the time to appearance of the flush, the exact area, the time to disappearance, and associated symptoms (overt sweating, swelling, pruritus, and pain) were noted.

Referring physicians were asked to enter details into a database concerning initial presentation, investigations, treatment, outcome, and last follow-up based on the patient's medical records.

This retrospective study was deemed to be exempt from ethical approval by the institutional clinical trials review board "CPP V Sud Méditerranée" due to the retrospective and noninterventional nature of the study. Two of the cases included had been published previously as case reports by members of the Frey Syndrome Collaborators.<sup>6,7</sup>

### Statistical Analyses

Quantitative variables were described as median and first and third quartiles.  $\chi^2$  or Fisher exact tests (if  $n < 10$ ) were used to compare frequencies. Student *t* and Mann-Whitney tests were used to compare quantitative data according to the normality of the distribution (Shapiro-Wilk test, skewness, and kurtosis). Effect sizes were calculated using the OR with 95% CI for significant  $\chi^2$  or Fisher exact tests and Cohen *d* for significant *t* or Mann-Whitney tests. Cohen test defined effect sizes as "small" ( $d = .2$ ), "medium" ( $d = .5$ ), and "large" ( $d = .8$ ).<sup>8</sup> *P* values of  $<.05$  were considered significant. All statistical analyses were performed using Stata v 10.0 for Macintosh (StataCorp, College Station, Texas).

## Results

Forty-eight children were included (9 in a primary or secondary care setting, 39 in tertiary pediatric centers); 27 were male (sex ratio 1.29) (Table I). Instrumented deliveries were mostly traumatic, with visible marks at birth in 68% of these patients (Figure 1, A). Neonatal marks were bilateral in 63% of instrumented delivery cases and unilateral in 37% of cases. Frey syndrome development was mostly ipsilateral (86% of cases) in cases born with a unilateral mark. Four neonates had another birth complication: broken collarbone, ocular hematoma, cephalohematoma, and eyelid edema.

One infant had a familial auriculotemporal nerve syndrome: her sister presented the same disease with milder symptoms. They both had a nonassisted vaginal delivery

**Table I.** Descriptive characteristics of the 48 patients with infantile Frey syndrome

Demographics	
Sex ratio (male:female)	1.29
Age at inclusion (mo)	57 (15-97)
Term (wk of amenorrhea)	39 (38-40)
Birth weight (g)	3250 (3000-3490)
Vaginal delivery	87%
First delivery	77%
Instrumental delivery	67%
Visible marks	68%
Other complications	11%
Forceps	58%
Spatula	39%
Vacuum	19%
Clinical characteristics	
Age at onset (mo)	5 (4.25-6)
Age at food diversification (mo)	5 (4-6)
Time for onset (min)	1 (0.5-3)
Duration (min)	15 (10-30)
Unilateral	73%
Bilateral	27%
Jugal area	68%
Temporal area	64%
Pretragal area	60%
Malar area	51%
Ear (auricle)	28%
Mandibular area	17%
Labial commissure area	15%
Flush	100%
Warmth	27%
Sweating	10%
Pruritus	6%
Hypersalivation	4%
Outcomes	
Duration of follow-up (mo)	25 (3-55)
Duration of symptoms (mo)	51 (11-81)
Stability	23%
Recovery	20%
Age at recovery (mo)	9 (7-9)
Regression	57%
Age at regression (mo)	24 (24-48)

Continuous variables are reported as the median (Q1-Q3).

but with a long period of labor. A history of asthma, allergic rhinitis, atopic dermatitis, and food allergy was reported in 24%, 16%, 21%, and 8% of patients, respectively.

Median age at onset corresponded to that of food diversification. Facial flush was unilateral in most cases (Figure 1, B-G). In unilateral cases, repartition between the right and left sides was essentially equal (16 right side, 19 left side). Topographic distribution of the flush involved mainly the jugo-temporal area. Flush was always reported, but associated with sweating in only 10% of cases. Fruits or fruit purees were cited as the most common initial trigger for 31 children, milk for 3 children, and all food types for 11 children.

### Diagnosis and Outcomes

Evaluations and outcomes are described in Tables I and II. In most cases, the first physician consulted by the parents was a pediatrician. Diagnosis was made at the first consultation in 20% of children, and the others remained without an established diagnosis. Allergy investigations were performed in 40% of cases during this first consultation. Dietary

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