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Episodic angioedema with eosinophilia (Gleich syndrome) in children: a clinical review.

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53 **i. Conflict of interest**

54 Matthieu Groh has consulting fees from GlaxoSmithKline and AstraZeneca; Guillaume Lefèvre
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63 **iii. Abstract and keywords**

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65 **Background:** Episodic angioedema with eosinophilia (EAE, Gleich syndrome) is a rare disease,
66 consisting of recurrent angioedema with hypereosinophilia and frequent increased serum
67 immunoglobulin M levels. Less than 100 patients have been reported, mainly adults, sometimes
68 with underlying lymphocytic variant of hypereosinophilic syndrome (HES_L). The aim of this study
69 was to identify and describe pediatric cases.

70 **Methods:** We performed a retrospective study of all pediatric cases of EAE referred within the
71 French National Referral Center for Hypereosinophilic Syndrome (CEREO). Next, the PRISMA
72 guidelines were applied in order to perform a systematic review (data sources: PubMed, Web of
73 Science).

74 **Results:** Among the two reported and 15 previously published cases of EAE occurring in children,
75 the main clinical findings mimicked those of adults, including recurrent angioedema, hives and
76 weight gain. The median time between the first angioedema flare and the diagnosis of EAE was
77 five years in published cases. Hypereosinophilia was constant, usually worsening with each attack,
78 but seldom disappeared between flares. Total IgM serum levels were elevated in 16 patients. Four
79 children had evidence of abnormal CD3-CD4⁺ T-cells. First-line therapy relied on oral
80 corticosteroids in all patients, and further lines (used in five patients) included interferon- α ,
81 methotrexate and ciclosporin. Two children developed eosinophilic myocarditis during follow-up.

82 **Conclusion:** Pediatricians should be aware that EAE is a diagnosis to consider in children. T-cell
83 immunophenotyping is warranted in this setting. Prognosis seems fair, yet eosinophil-related
84 organ damage may occur in patients with persistent eosinophilia.

85 **Keywords:** Episodic angioedema with eosinophilia, Gleich syndrome, children.

87 **iv. Main text**

89 **Introduction:**

90 Eosinophilia may occur in numerous dermatologic conditions, *e.g.* atopic dermatitis, drug-induced
91 rash, bullous pemphigoid, eosinophilic cellulitis (Wells' syndrome), primary epidermotropic T-

cell lymphoma and mastocytosis [1]. Gleich syndrome, also known as episodic angioedema with eosinophilia (EAE), is a rare disease consisting of recurrent episodes of angioedema associated with concomitant hypereosinophilia and frequent increased serum Immunoglobulin M (IgM) levels [2]. To date, less than 100 patients have been reported, mainly at adult age.

Since the first set of hypereosinophilic syndrome (HES) classification criteria established by Chusid *et al.* in 1975, several updates have been provided over time. Nowadays, the two main – and partially redundant – classifications of HES are those endorsed by the WHO and the International Cooperative Working Group on Eosinophil Disorders (ICOG-EO). Briefly, the ICOG-EO classification was established in 2011 and differentiates various HES subtypes. In neoplastic (or clonal) HES (HES_N), gene rearrangements lead to clonal eosinophilia, while reactive HES (HES_R), aggregates all conditions – including the lymphocytic variant of HES, (HES_L) – in which non-clonal eosinophilia is driven by Th2 cytokines). Last, idiopathic HES (HES_I) is considered in case of negative etiological workup [3,4]. Specifically, HES_L is a chronic clonal indolent T-cell lymphoproliferative disorder in which mature peripheral T cells secrete high amounts of Th2-related cytokines (including interleukin IL-5, IL-4, IL-13) and GM-CSF, thereby leading to eosinophilia and subsequent eosinophil-related organ damage.

According to the ICOG-EO classification, EAE might represent a subgroup of HES, yet several cases of EAE occurring in patients with HES_L have been reported [5-7]. Here, we report on two cases of EAE occurring in children (including one HES_L-associated EAE). We also performed a literature review of all EAE pediatric cases reported to date.

Methods:

We performed a retrospective study of all pediatric (<18 years old) cases referred and/or managed within the French National Referral Center for Hypereosinophilic Syndrome (CEREO). Inclusion criteria were: (i) episodic and recurrent angioedema, (ii) concomitant blood hypereosinophilia (*i.e.* eosinophil granulocytes higher than 1.5 G/L at least twice) and (iii) the exclusion of an alternate diagnosis for both angioedema and eosinophilia. Data at diagnosis of EAE and during follow-up were collected using a standardized data extraction form. Next, the PRISMA guidelines were applied in order to perform a systematic review of all pediatric cases of EAE (<18 years old): we searched for original articles, case reports, and letters to editor reporting pediatric cases of EAE in two electronic databases (PubMed and Web of Science) using the following keywords (both as free text and MeSH terms): “episodic angioedema with eosinophilia”, “Gleich syndrome”. Relevant articles were first selected based on their titles. Abstracts and full-texts of selected

abstracts were subsequently reviewed, and references screened for additional articles. Only articles with full text available in English, Spanish or French were considered (Figure 1). Descriptive analysis involved frequencies and percentages for qualitative variables and median [minimum-maximum] as appropriate for quantitative variables.

Results:

Cases referred and/or managed within the CEREO: four cases were screened.

Case 1: A 7-year-old boy presented with recurrent angioedema flares affecting the left side of the face (cheek or eyelid) (Figure 2) with weight gain of 1 kg (5% of weight) during attacks but without fever. At referral, he had experienced a total of 11 attacks (duration of each flare: two to five days) and the time between attacks ranged from one to four weeks. Absolute eosinophil count (AEC) was normal (0.3 G/L) four months before the first attack and increased thereafter above normal thresholds during each flare (reaching 1.7 G/L at peak). Other routine hematological and biochemical tests were unremarkable, and etiological workups for both eosinophilia and angioedema (including total IgE and IgM levels, tryptase, C-reactive protein, complement fractions (C3, C4, CH50), C1-inhibitor, toxocariasis serology, parasitic stool analysis, prick-tests and T-cell immunophenotyping) were negative. Orbital magnetic resonance imaging (MRI) was normal and the diagnosis of EAE was retained. The first two flares had resolved spontaneously within 48-72 hours. Thereafter, the patient was successfully treated during each flare with recurrent bursts of corticosteroids (prednisone up to 2mg/kg/day), leading a rapid decrease of the AEC under 1.0 G/L. After six months of recurrent attacks, the angioedema spontaneously disappeared, and AEC returned to normal values, with one-year of follow-up after the last attack.

Case 2: A 16-year-old girl with a past medical history of non-atopic asthma and short-term idiopathic thrombocytopenic purpura at the age of eight (treated with intravenous immunoglobulins) presented with a 6-month history of recurrent angioedema attacks affecting both the face and upper and lower limbs along with hives, headaches, moderate abdominal pain, and weight gain (reaching up to 2 kg - 3%) but without fever. Flares lasted from a few hours to five days, and the time between attacks ranged from one to four weeks. All attacks spontaneously resolved. AEC ranged between 2 and 25 G/L, serum IgM serum level was markedly elevated (12.6 g/L; normal range: 0.5-3 g/L), while serum total IgE, IgG, IgA, vitamin B12, vitamin E, tryptase levels and stool analysis were normal or negative. Troponin level, electrocardiogram, echocardiography, abdominal ultrasonography, cerebral MRI and lung CT-scan were unremarkable. Blood T-cell immunophenotyping identified an aberrant CD3-CD4⁺ T cell

156 population, (2% of total T-cells). The same results were found at one-year of follow-up, yet the
157 search for clonal rearrangement of the γ chain of the TCR always tested negative. The diagnosis of
158 HES_L-associated EAE was retained. Fearing adverse effects, the patient refused CS therapy. Due
159 to weekly recurrences of attacks, Peg-interferon alfa-2a (45 ug/week) was finally started after two
160 years of disease duration. With three months of follow-up after onset of treatment, she is now free
161 of symptoms with normal AEC.

162 The two others cases managed within the CEREO have already been published and are described
163 with the literature review in Table 1.

164 **Literature review**

165 Fifteen children (10 males, median age 10 years [range 2.5-17]) with Gleich syndrome living in
166 Europe, Asia or the United States were identified (Table 1) [2,5-13]. The median time between the
167 first angioedema flare and the diagnosis of EAE was five years (data available for n=11 patients).
168 Overall, the clinical picture seems to be similar to that reported in adults, consisting mainly of
169 recurrent angioedema of the face and/or extremities (n=15), sometimes of the trunk (n=4),
170 associated with other dermatological manifestations in more than half of the cases such as hives,
171 urticaria or eczema (n=11), and weight gain (n=7, when specified). Seven patients had extra-
172 dermatological manifestations, including gastrointestinal symptoms (n=1, consisting of abdominal
173 pain, diarrhea, nausea), splenomegaly (n=5), and arthralgia (n=1). Four children had fever during
174 attacks. The median time between flares was four weeks [range 1-4], and the median AEC was 28
175 G/L [range 3.3-57]. Serum total IgM levels were increased in all children, while serum total IgE
176 levels were increased in 8/13 children. Among the seven children for whom T-cell
177 immunophenotyping was performed (including the search for an aberrant HES_L-population), three
178 showed evidence of abnormal CD3-CD4⁺ T-cells population. Antihistamines drugs were always
179 ineffective, contrasting with short-term corticosteroids (0.5-1mg/kg of daily prednisone). Hence,
180 the latter enabled rapid clinical improvement in all 12 treated children who received such
181 medication and led to the normalization of AEC in 7/8 patients for whom these data were
182 specified. Of note, the remaining three patients had spontaneous (*i.e.* without corticosteroids)
183 resolution of EAE flares but their AEC did not return within the normal range [2,7,11].
184 Four children had further-line treatments: interferon- α (n=2), methotrexate (n=1), ciclosporin
185 (n=1). In line with the two cases reported herein, no child had life-threatening or end-organ
186 damage at disease onset, yet two developed eosinophilic heart involvement during follow-up: one

adolescent developed four years after disease onset an asymptomatic eosinophilic myocarditis, and one child developed sixteen years after disease onset a myocarditis fibrosis.

Discussion:

EAE was first described by G.J Gleich *et al.* in 1984 in four adult patients [2]. Since then, less than one hundred cases have been reported and pediatric cases are scarce [6]. Overall, the two cases reported here and a subsequent literature review support the fact that the clinical picture of pediatric cases mimics that of adult patients, with predominantly weight gain, angioedema, urticaria, gastro-intestinal and joint involvements, with spontaneous remission and recurrence thereafter [6]. Fever (contrasting with mild biological inflammatory parameters) is likely to occur in a non-negligible proportion of patients, but the severity of angioedema flares seems to be mild (neither life-threatening features - *e.g.* severe laryngeal involvement - nor Intensive Care Unit admission were reported). By definition, hypereosinophilia (HE) is constant, usually growing along attacks, but can disappear between flares. Total IgE and polyclonal IgM levels are frequently elevated, while underlying HES_L, detected in 40% of adults, is associated with a shorter time to flare while on effective treatment [6].

The cases reported herein stress the potential pitfalls of the management of angioedema in children. First, the time to diagnosis was long (six months in both cases, reaching up to five years in previous reports). Although flare triggers were lacking and antihistamine drugs were ineffective, angioedema crises were initially misdiagnosed as histaminergic angioedema. Hence, non-inducible and recurrent angioedema flares (especially when antihistamine drugs fail to curb disease manifestations) should lead to broader investigations, including the search for bradykinin-mediated angioedema, mastocytosis, cryopyrinopathies and eosinophil-mediated angioedema (including Gleich syndrome and helminthiasis, when appropriate). Although skin biopsies can show eosinophilic infiltrate and deposition of eosinophil granule proteins, histology is not mandatory to ascertain the diagnosis of EAE.

Next, T-cell immunophenotyping was performed in less than half of previously reported cases of pediatric EAE, and we cannot rule out that the prevalence of HES_L amongst childhood EAE patients might be underestimated. Although HES_L-associated EAE has been extensively reported in adults, the case reported herein, to our knowledge, is the fourth pediatric case CD3⁺CD4⁺ HES_L [6]. Since patients with abnormal T-cell phenotypes (i) exhibit a peculiar phenotype (with more frequent peripheral lymphadenopathy, urticarial papules and a shorter time to flare); (ii) are at risk of acute transformation to an aggressive angioimmunoblastic T-cell lymphoma [6], T-cell

immunophenotyping (dedicated to the search of HES_L-defining T-cell subsets, *i.e.* CD3⁺CD4⁺, CD3⁺CD4⁺CD7⁻ or CD3⁺CD4⁺CD8⁺TCR^{αβ}⁺) is warranted in all cases of EAE, even during childhood. Moreover, CD3⁺CD4⁺ T cells can be present at low threshold values (0.5-1% of total T cells) and can cycle over time, leading to false negative results. Hence, if clinical manifestations are suggestive of HES_L, T cell phenotyping should be repeated if in doubt [5]. Conversely, since EAE has been exclusively reported in HES_I and HES_L (without any HES_N-related case to our knowledge), bone marrow examination and genetic tests (*e.g.* the search for FIP1L1-PDGFR_A fusion transcript) are likely not first-line investigations to be performed in the setting of EAE.

The pathophysiology of EAE is still unclear. Cyclic elevations of Th2-related cytokines (namely IL5 and IL13) and subsequent rise of eosinophils have been reported during flares [7]. Moreover, Platelet-Activating Factor, leucotrienes, and major basic protein (all of which are produced by eosinophils) are likely to increase vascular hyperpermeability, thereby leading to angioedema and weight gain. Lastly, it has recently been evidenced in four untreated HES_L-EAE patients that eosinophils are not the only cells involved in the disease's pathophysiology. Both neutrophil and lymphocyte absolute counts increase in a cyclic pattern that parallels that of eosinophils, and indirect evidence (*e.g.* mild increases of mast cells in skin and bone marrow, cyclic elevation of tryptase and stem-cell factor) also suggests that mast cells could be involved [7].

Although with limited follow-up, but in line with previously published work, our data suggest that EAE carries a fair prognosis. Yet, although the severity of angioedema flares was mild, Wright *et al.* reported the case of a child who developed severe eosinophilic endomyocardial fibrosis and mitral valve disease (requiring prosthetic valve replacement) 16 years after disease onset [14], and Abisror *et al.* reported the case of an adolescent with asymptomatic eosinophilic myocarditis [6]. Of note, both patients did not receive long-term therapy and had persistent eosinophilia between angioedema flares. Hence, as with any other chronic eosinophilic disorder, a systematic search for other eosinophil-related involvement (including troponin level, electrocardiogram and echocardiography) should be performed at diagnosis of EAE and during follow-up in case of persistent eosinophilia. Moreover, although not reported yet in pediatric patients, long-term monitoring is warranted for HES_L-related EAE patients given the risk of acute transformation to angioimmunoblastic T-cell lymphoma [6].

There is no definite algorithm for the management of EAE. Due to their dual suppressive effects on both eosinophil proliferation and Th2-cell cytokine production (such as IL5), corticosteroids

250 remain the first-line therapeutic option. Depending on disease severity, they can either be used
251 occasionally during flares or continuously. If long-term therapy is initiated, one should seek for
252 the minimal efficacy dose, especially in children where long-term corticosteroids use is associated
253 with significant morbidity (including growth delay). Further-line treatments can be considered on
254 a case-by-case basis. These usually rely on Interferon- α (that leads to partial or complete
255 remission in about 80% of adult-EAE patients, but is also associated with frequent side-effects that
256 limit its use in daily care) or methotrexate. Ciclosporin A might be another option, yet renal
257 toxicity is a concern in children requiring long-term maintenance therapy [5]. Last, IL5-targeted
258 biologics (e.g. mepolizumab and benralizumab) are attractive options in this setting. Yet, data
259 regarding their use are limited during childhood and, to date, access to these drugs is limited
260 outside the scope of eosinophilic asthma [15].

261 **In conclusion**, pediatricians should be well aware that EAE (Gleich syndrome), although being a
262 rare disease, is a diagnosis to envisage in children presenting with recurrent attacks of angioedema
263 and HE. Patients should be thoroughly investigated, including T-cell immunophenotyping. Short-
264 term glucocorticoids are highly effective, yet some patients with frequent crises and/or extra-
265 dermatological manifestations require long-term therapy. Disease prognosis seems fair, yet HES_L
266 patients are at increased risk of angioimmunoblastic T-cell lymphoma transformation, and
267 eosinophil-related organ damage (including heart involvement) may occur in patients with
268 persistent eosinophilia. Given the rarity of this syndrome, EAE should ideally be managed in (or
269 in collaboration with) centers with established expertise in the field of HES.

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271

272 **vi. References**

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vii. Tables

Table 1: pediatric cases reported in literature since 1984.

Cases, Study, Year of publication	Age (years) /Sex	AEC [†] max (G/L)	Aberrant T-cell population (% of total T-cells)	High IgM/ High IgE serum levels	Symptoms	Time period between attacks (weeks)	Treatment	Follow-up duration and outcome/ complications
1 Gleich et al ² , 1984	4/M ^{††}	50	NA ^{§§}	Y ^{†††} /N [‡]	EAE [§] (face, trunk, all 4 limbs), fever	2	Recurrent CS [‡]	None at 5 years
2 Gleich et al ² , 1984	7/F ^{¶¶}	57	NA	Y/N	EAE (face, limb extremities), hives, fever, splenomegaly, WG ^{¶¶}	4-6	Recurrent CS	Endomyocardial fibrosis at 16 years (interferon α started)
3 Gleich et al ² , 1984	16/M	28	NA	Y/N	EAE (face, all 4 limbs), hives, WG	4	N	None at 30 years
4 Katzen et al ⁹ , 1986	2.5/F	32	N	Y/Y	EAE (face, trunk, all 4 limbs) fever, WG	4	Recurrent CS	None at 1 year
5 Hill et al ¹⁰ , 1986	12/M	48	NA	Y/NA	EAE (face, all 4 limbs), urticaria	3	Recurrent CS	None at 9 years

6 Lassalle et al ¹¹ , 1990	10/M	12	NA	Y/Y	EAE (face, lower-limbs, pubis), urticaria, WG	4	N	None at 12 years
7 Lassalle et al ¹¹ , 1990	7/M	4.9	N	Y/N	EAE (face, all 4 limbs) hives, splenomegaly	4	N	None at 15 years
8 Armstrong et al ¹² 2001	9/ M	6.7	NA	Y/Y	EAE (face) hives, WG, splenomegaly	4	Recurrent CS	None at 5 years
9 Garcia Bravo et al ¹³ 2005	17/F	3.3	NA	Y/NA	EAE (hands, feet, face)	4	Recurrent CS	None at 3 years
10 Khoury et al ⁷ , 2015	10/M	18.4	CD3-CD4+ at adult age	Y/Y	EAE (face, trunk), hives, fever, WG,	4	Recurrent CS	None at 15 years
11 Liu et al ⁸ , 2017	12/F	43	NA	Y/Y	EAE (face, all 4 limbs, trunk), arthralgias, WG, urticaria	4	Recurrent CS	None at 2 years
12 Lefevre et al ⁵ , 2018 Abisror et al ⁶ , 2019	5/F	52	6% CD3-CD4+	Y/Y	EAE (face, limb extremities), hives,	NA	Recurrent CS ciclosporin	None at 9 years
13 Lefevre et al ⁵ , 2018	16/M	18	6% CD3-CD4+	Y/Y	EAE (face, limb extremities), eczema, splenomegaly	NA	Recurrent CS	None at 5 years
14 Abisror et al ⁶ , 2019	11/M	18	6% CD3-CD4+	Y/N	EAE (face, limb extremities),	2	Recurrent CS, interferon α	None at 3 years

					hives, eczema, splenomegaly			
15 Abisror et al ⁶ , 2019	13/M	53	N	Y/Y	EAE (face, limb extremities) abdominal pain, diarrhea, nausea	1	Recurrent CS	Asymptomatic myocarditis at 4 years (methotrexate started)
16 present case	5/M	1.7	N	N/N	EAE (face), WG	1-4	Recurrent CS	None at 1 year
17 present case	16/F	25	2% CD3-CD4+	Y /N	EAE (face, all 4 limbs), hives, WG, abdominal pain	1-4	Recurrent CS, interferon α	None at 2 years

Abbreviations: [†]AEC: absolute eosinophilia cell count; [‡]CS: corticosteroids; [§]EAE: episodic angioedema; F[¶]: female; M^{††}: male; N^{‡‡}: no; NA^{§§}: not applicable; WG^{¶¶}: weight gain; Y^{†††}: yes.

viii. Figure legends

Figure 1: Flow chart showing the search strategy.

Figure 2: Angioedema affecting the upper and lower-left eyelids.



