

Hyper-IgE syndrome presenting with early life craniosynostosis in monozygotic twin sisters

To the Editor,

Autosomal dominant pathogenic variants in signal transducer and activator of transcription 3 (STAT3; OMIM*102582) are implicated in both autosomal dominant hyper-IgE syndrome (AD-HIES; OMIM*147060) and autosomal dominant autoimmune disease, multisystem, infantile-onset type 1 (ADMIO1; OMIM*615952). Gain-of-function variants (GoF) are described to be causative of ADMIO1, whereas dominant negative (DN) variants cause AD-HIES.^{1,2} Indeed, recent articles have demonstrated that heterozygous loss-of-function (LoF) variants underlie AD-HIES through a dominant negative effect rather than haploinsufficiency.³ AD-HIES results in a syndrome with both hematopoietic and nonhematopoietic features, including a significant issue with bone remodeling.⁴ HIES can be caused by pathogenic variants in other genes such as *IL6R*, *IL6ST*, *ZNF341*, *SPINK5*, *PGM3*, *CARD11*, *TGFBR1*, *TGRBR2*, *BCL11B*, and *ERBB2IP*.⁵ STAT3 is a signaling molecule acting downstream of many cytokine receptors. Aberrant transduction of these pathways explains the multisystem manifestations of the syndrome comprising skeletal and connective tissue abnormalities, dermatitis, autoimmunity disorders, pulmonary disease, vasculopathy, and immunodeficiency. Many of the immunological abnormalities, such as high IgE levels, low levels of inflammation, atopy, and recurrent staphylococcal infections, are due to impaired IL-6 pathways, a proinflammatory cytokine crucial for Th-17 and early stages of T follicular helper (Tfh) cell differentiation.⁶⁻⁸ A deficiency in Th-17, which releases antimicrobial peptides and produce the IL-17 cytokine family, is implicated in *Staphylococcus aureus*, *Candida*, and gram-negative infections. Thus, decreased IL-17 production may explain the predisposition to epithelial and lung infections as keratinocytes and bronchial epithelial cells require IL-17A for antistaphylococcal β -defensin secretion.⁹ In addition, recurrent sino-pulmonary infections in association with impaired connective tissue remodeling lead to pulmonary structural abnormalities.^{8,9} The most consistent laboratory finding in HIES is an elevated serum-IgE level (2000–100,000 IU/mL).^{9,10} Total immunoglobulin and white blood cell counts are usually normal, although common eosinophilia and relative neutropenia have been observed. Leukocytosis and acute phase reactants often fail to increase in response to infection.^{10,11} Current therapies include antistaphylococcal antibiotic prophylaxis together with antiseptic washes to prevent dermatological and pulmonary infections and antifungals to treat

and prevent mucocutaneous *Candida*, while mold-active antifungals are considered when parenchymal lung disease is present to prevent aspergillosis.⁸ Patients with hypogammaglobulinemia and/or functional antibody deficiency or impaired memory immunity can benefit from immunoglobulin replacement therapy.⁹ Other treatments include Dupilumab, especially for atypical cutaneous manifestations or severe eczema.^{5,12} Hematopoietic stem cell transplantation also appears promising in immune reconstitution and pulmonary and dermatological symptoms; however, postsuccessful transplant, patients have continued to develop muscular skeletal complications (fractures, scoliosis).⁸

Craniosynostosis results from the premature closure of one or more sutures of the skull. Craniosynostosis can be nonsyndromic, when it is an isolated finding, or syndromic, i.e., associated with other signs such as anomalies of the face, skeleton, or nervous system and developmental delay. Craniosynostosis can be caused by pathogenic variants in the following genes: *FGFR2*, *FGFR3*, *FGFR1*, *TWIST1*, *TCF12*, *ERF*, *ALPL*, *FBN1*, *SKI*, and *EFNB1*. Half of the patients with craniosynostosis carry a de novo variant.^{13,14} Craniosynostosis has been described in some cases with AD-HIES,¹⁵⁻¹⁷ as well as Arnold Chiari type 1 malformation.¹⁵ Of note, craniosynostosis is more frequent in HIES caused by IL6ST pathogenic variants.¹⁸

Craniosynostosis and dental abnormalities are caused by a disturbance in a shared IL-6, IL6R./IL-11/IL-11RA/glycoprotein gp130 (GP130)/STAT3-driven process. Sutural closure depends on the coordinated regulation of the apposition and resorption by osteoblasts and osteoclasts, respectively. Thus, STAT3 deficiency explains the premature, often prenatal fusion of some or several calvarial bones. As a result, the lack of space limits brain growth and the compensatory increase in other sutures causes skull deformation.¹⁹

We herein report two patients diagnosed at 5 years of age with AD-HIES. Patients were monozygotic twin sisters born at 33 weeks without major complications after a bichorionic, triamniotic pregnancy following in vitro fertilization. Parents and the male triplet were healthy. The twin sisters presented in early infancy with recurrent otitis media with chronic middle ear effusion and pansynostosis presenting with raised intra-cranial pressure just before 4 years of age.

Case 1 developed severe respiratory syncytial virus (RSV) bronchiolitis at 6 months requiring noninvasive ventilation (NIV) with

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continuous positive airway pressure for 1 week. Then, she suffered from recurrent otitis media almost once a month, requiring antibiotics. Following the detection of chronic middle ear effusions, she required grommets at 3 and half years of age, which fell out 6 months later, requiring new insertions. She had 2 episodes of *Staphylococcus aureus* skin infection on the genital areas and on her face. She also had intermittent episodes of conjunctivitis. Papilloedema, with associated headaches, was identified at the age of 3 years and 9 months, and imaging identifying pansynostosis. At 4 years, she had a correction of the pansynostosis with a posterior vault expansion with calvarial remodeling, complicated by a wound infection, which required a further operation to debride the infected soft tissue. During the same period, she had a furuncle on the left foot. At 4 years and 8 months, she was diagnosed with a pulmonary abscess of the upper right lobe (Figure 2) with pleural effusion. Culture yielded methicillin-resistant *S. aureus* first treated with vancomycin, switched to cefuroxime and azithromycin due to resistance, and then switched to linezolid due to clinical impairment. Subsequently, she developed an intolerance to linezolid, due to lactic acidosis, and the treatment was interrupted before being switched to ciprofloxacin and rifampicin for a further 5 weeks. During this episode, she required NIV and surgical drainage. At this time, an immunology workup was initiated and showed normal total IgG, IgA, and IgM, but the total IgE level was increased (1651 KU/l). Vaccine antibodies were low for all vaccine antigens, despite normal vaccination history for age but with good responses following booster vaccination. She also had decreased switched memory B cells. The dihydrorhodamine and lymphocyte proliferation tests were normal. Genetic analyses were organized (see Table 1).

A few weeks after the end of antibiotic treatment for the pulmonary abscess, she had a relapse of pneumonia in the same place, which was treated with oral rifampicin and ciprofloxacin. However, 2 weeks later, she developed a varicella pneumonia and was therefore treated with intravenous ciprofloxacin, rifampicin, and acyclovir. During the same period, she continued to have left ear secretions with a culture positive for *Candida albicans* and *Stenotrophomonas*.

Case 2 was hospitalized in the intensive care unit at 6 months of age for severe RSV bronchiolitis requiring NIV with continuous positive airway pressure for 3 days. She also had acute pyelonephritis caused by *Escherichia coli*, treated with 7 days of antibiotics. At 1 year, she had bronchitis. Then, she presented with recurrent otitis media, with a range of bacterial and candida species isolated. She benefited from the insertion of grommets at 3 years and 7 months. At 2 years, she presented with a first episode of pneumonia, which was treated with oral antibiotics. At almost 4 years, she had retrocardiac pneumonia, which was treated with oral antibiotics. She also had recurrent conjunctivitis and identification of papilloedema at 3 years and 9 months, with imaging showing craniosynostosis (see Figure 1). At 4 years, she underwent surgical correction of her pansynostosis by craniotomy, complicated by necrosis of the wound tissues, and 2 months later by an MRSA skull infection, requiring a further operation to debride the infected soft tissues and antibiotics with rifampicin and teicoplanin. Similarly, to her sister, at 4 years and

9 months, an immunology workup was initiated and showed normal total IgG, IgA, and IgM but increased IgE (2011 KU/l). The vaccine antibodies were low for all antigens, despite normal vaccination, and with partial responses following booster vaccinations. She also had decreased switched memory B cells. The dihydrorhodamine (DHR) and lymphocyte proliferation tests were normal (see Table 1). Genetic analyses were initiated.

Just after, at 4 years and 11 months, she developed a severe varicella infection complicated by pneumonitis and pericardial effusion, including an MSSA and group A *Streptococcus pyogenes* bacteremia and left axillary cellulitis. She was treated with debridement and fasciectomy of the armpit lesion, as well as with intravenous co-amoxicillin, clindamycin, and acyclovir. One month later, she developed cellulitis on a wasp sting from 2 weeks before, treated with local fusidic acid for 10 days. Two months after the varicella infection, she developed a new skin infection on the scar under the armpit, treated with surgical drainage and oral clindamycin.

Whole exome sequencing with bioinformatics targeted analysis on 92 genes implicated in errors of immunity (Appendix S1) was performed. The results showed a likely pathogenic heterozygous de novo *STAT3* missense variant, c.1976T>A, p.Ile659Asn in both sisters. Familial segregation using Sanger sequencing did not detect the variant in the parent's and brother's blood.

The *STAT3* variant c.1976T>A, p.Ile659Asn was first reported in the literature in an abstract in 2019 where the authors clearly stated that further studies were needed to understand the mechanism causing the phenotype.²⁰ It has been reported in ClinVar Database in 2021 as pathogenic with the mention of *STAT3* gain-of-function diseases; nevertheless, to our knowledge, no functional analysis has been conducted on the variant; and it was not included in the recent review about *STAT3*-HIES variants.³ Therefore, it is difficult to assess the functional impact of the variant (GoF or DN); and it was not possible to perform a luciferase assay in our center. However, in our cases, the phenotype of the two sisters, associating recurrent respiratory tract infections, lung abscess, recurrent *Staphylococcus aureus* skin infections, craniosynostosis, hyperextensibility, and elevated IgE, is more compatible with HIES, despite the presence of musculoskeletal alterations (bone and connective tissue alterations), which can also be observed in *STAT3* gain-of-function variants.²¹ According to the NIH HIES scoring system (<https://bsolomon.us/app/hies-score/>),^{22,23} the two sisters had a score of, respectively, 31 and 34 points (see Table 2), making the diagnosis of HIES very likely.

This report highlights the difficulty to diagnose inborn errors of immunity early in life before the development of severe infections that can lead to long-term morbidity. Once, we had obtained the genetic diagnosis, we reviewed again the clinical history and ask the parents about other features of HIES; the two sisters had not presented with a newborn rash. They had a very mild eczema and no other characteristics of HIES. They had some dysmorphic features such as a prominent forehead and chin, deep-set eyes, and broad nose.

Classically, HIES first presents with pustular or eczematoid eruptions on the face and scalp, typically starting in the newborn

TABLE 1 Immunological parameters at first evaluation at 5 years of age.

		Normal values	Case 1	Case 2
White blood cells	G/l	5–14.5	11.8	8.4
Lymphocytes	G/l (%)	1.5–7.5 (25–59)	3.07 (26)	4.2 (50)
Neutrophils	G/l (%)	1.5–8 (23–64)	6.96 (59)	3.23 (39)
Eosinophils	%	0–5	0.24 (2)	0.48 (4)
Basophils	%	0–2	0	0
Platelet	G/l	168–392	555	297
Lymphocyte immunophenotyping				
Lymphocytes	/mmc	1100–5900	3638	4913
T cells	/mmc (% lymph tot)	780–2240	2396 (65.9)	3363 (68.4)
CD4	/mmc (% Tcells)	490–1640	1223 (51)	1701 (50.6)
CD4-naïve	/mmc (% CD4)	200–2500 (46–99)	875 (71.5)	1345(79.1)
CD4 RTE	/mmc (% CD4)	200–1700 (41–81)	645 (52.7)	1057 (62.2)
CD4 memory	/mmc (% CD4)		347 (28.3)	354(20.8)
CD4 CXCR5+	/mmc (% CD4 mem)		67 (19.4)	63 (17.7)
CD4 PD- 1+	/mmc (% CD4 mem)		126(36.4)	99(27.9)
CD4 ICOS+	/mmc (% CD4 mem)		58 (16.6)	60 (16.8)
CD4 CXCR3+	/mmc (% CD4 mem)		310 (89.5)	318 (89.8)
CD4-circulating memory TFH	/mmc (% CD4 mem)		1(0.2)	0
CD8	/mmc (% Tcells)	170–880	850 (35.5)	1270 (37.8)
CD4-CD8-	/mmc (% Tcells)		262(10.9)	310 (9.2)
CD4-CD8- TCRyδ+	/mmc (% CD4-CD8-)		176 (67.2)	166 (53.5)
TCRyδ	/mmc (% Tcells)	25–200	287 (12)	200 (5.9)
NK	/mmc (% lymph tot)	80–690	171 (4.7)	83 (1.7)
B cells	/mmc (% lymph tot)	200–1600	972 (26.7)	1224 (24.9)
CD27 +IgD+	/mmc (% B cells)	20–100 (5.2–20.4)	32 (3.3)	59 (4.8)
CD27-IgD+	/mmc (% B cells)	130–460 (47.3–77)	846 (87)	1055 (86.2)
CD27 +IgD-	/mmc (% B cells)	40–140 (10.9–30.4)	20 (2.0)	23 (1.9)
CD27-IgD-	/mmc (% B cells)	10–70 (2.3–11)	75 (7.7)	87 (7.1)
CD21lowCD38low	/mmc (% B cells)	10–40 (2.3–10)	17 (1.7)	15 (1.2)
CD38highIgM+	/mmc (% B cells)	10–40 (4.6–8.3)	0 (0.0)	1 (0.1)
CD38highIgM-	/mmc (% B cells)	0–30 (0.6–5.3)	0 (0.0)	1 (0.1)
Monocytes	/mmc (% mononuclear cells)	200–800	146 (3.9)	222 (4.3)
Myeloid dendritic cells	/mmc (% mononuclear cells)		24 (0.6)	27 (0.5)
Conventional dendritic subpopulation	/mmc (% mononuclear cells)		2(0.1)	2(0)
Dendritic cells CD141+	/mmc (% mononuclear cells)		0	0
Inflammatory dendritic subpopulation	/mmc (% mononuclear cells)		10(0.3)	19 (0.4)
Plasmacytoid dendritic cells	/mmc (% mononuclear cells)		3(0.1)	9 (0.2)
Lymphocyte proliferation tests				
Anti-CD3			Positive	Positive
Tetanus			Positive	Positive
<i>Candida albicans</i>			Positive	Positive
Phytohemagglutinin			Positive	Positive
<i>S. pneumoniae</i>			Positive	Positive
DHR 123			Normal	Normal

(Continues)

TABLE 1 (Continued)

				Normal values	Case 1	Case 2	
Ig levels							
IgG		g/l		5.6–15.4	9.37	9.90	
IgA		g/l		0.27–1.66	0.76	0.69	
IgM		g/l		0.32–1.39	1.17	1.07	
IgE		kU/l		<155	1651	2011	
Vaccine antibodies				Pre ^a	Post ^a	Pre ^a	Post ^a
Tetanus	UI/l	>100	<100	1362	<100	112	
Diphtheria	UI/l	>100	<100	322	<100	<100	
Measles	UI/l	>150	<50	>5000	63	>5000	
Pneumococcal serotypes included in the Prevenar13 (3 serotypes tested)	mg/l	>0.5 for 3/3 serotypes	1/3	3/3	1/3	3/3	
Pneumococcal serotypes not included in the Prevenar13 (3 serotypes tested)	mg/l	>0.5 for 3/3 serotypes	1/3	3/3	1/3	3/3	
Genetic analysis							
Whole exome sequencing				STAT3 c.1976 T> A, [p.Ile2659Asn]; hemi-heterozygote	STAT3 c.1976 T> A, [p.Ile2659Asn]; hemi-heterozygote		

Note: Dihydrorhodamine (DHR) 123 test: immunological test evaluating the NADPH complex in neutrophils stimulated with phorbol myristate acetate and incubated with DHR 123. DHR 123 is oxidized by hydrogen peroxide (produced in the presence of a normal NADPH oxidase–myeloperoxidase system in neutrophils) to rhodamine 123, which emits fluorescence. The fluorescence of each cell is then assessed by flow cytometry as a surrogate measure of NADPH oxidase activity. The mean fluorescence intensity of rhodamine 123 has been shown to quantitatively correlate with reactive oxygen intermediate production.

Bold values are abnormal results.

^aBooster vaccination with dTPa-IPV, measles, mumps, and rubella, and the plain polysaccharide 23-valent pneumococcal vaccine (Pneumovax®) were given following the first laboratory evaluation, and a new vaccine serology was performed 1 month later.

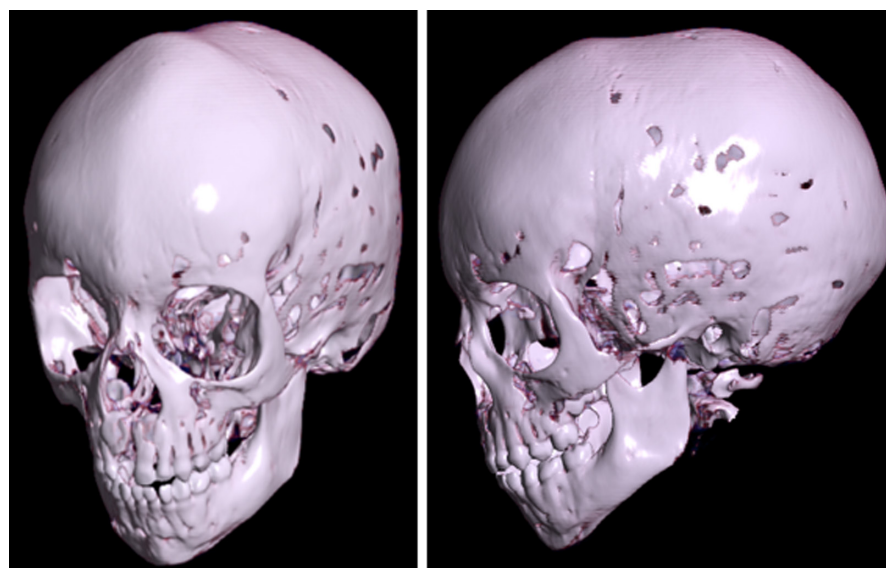


FIGURE 1 Three-dimensional computed tomography scan of oblique (left) and lateral (right) views showing pansynostosis in case 2. Note that thin areas of calvarium are projected as bony defects because of the reconstruction algorithm. Three-dimensional CT, oblique (left) and lateral (right) views showing pansynostosis in the second sister. Note that thin areas of calvarium are projected as bony defects because of the reconstruction algorithm.

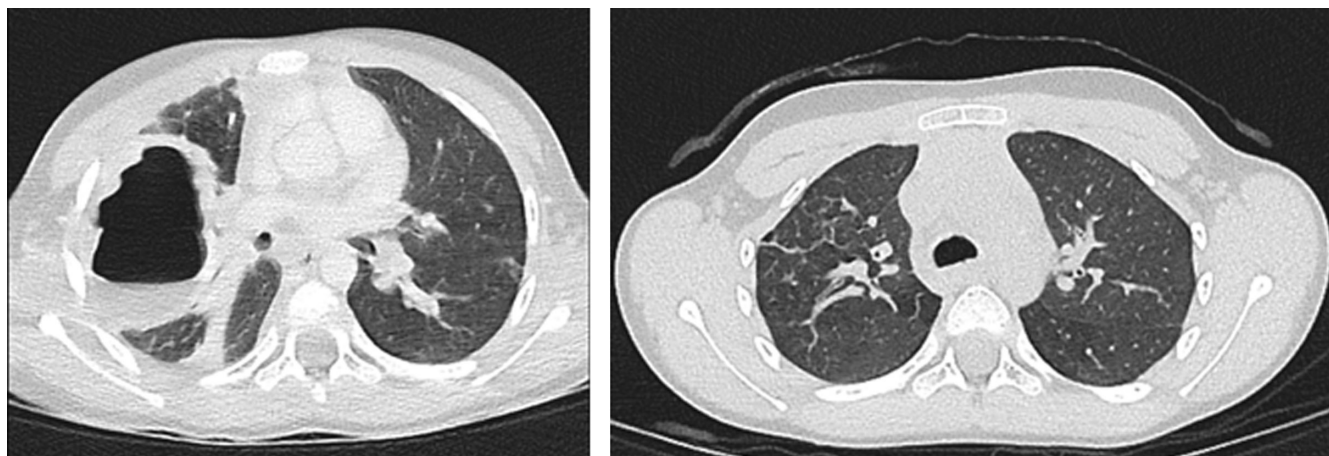


FIGURE 2 Computed tomography scan demonstrating upper right lobe pulmonary abscess pre-treatment (4 years and 9 months) (left) and sequelae with fibro-retractile changes post-treatment (5 years and 10 months) (right) in case 1. CT demonstrating upper right lobe pulmonary abscess pre-treatment (4 years and 9 months) (left) and sequelae with fibro-retractile changes post-treatment (5 years and 10 months) (right) in the first sister

TABLE 2 Scoring system with clinical and laboratory tests for patients with suspicion of HIES.²²

CLINICAL FINDINGS up to 5 years	CASE 1	CASE 2
Highest serum-IgE level (IU/ml)	8	10
Skin abscesses	0	2
Pneumonia (episodes over lifetime)	4	4
Parenchymal lung anomalies	0	0
Retained primary teeth	0	0
Scoliosis, maximum curvature	0	0
Fractures with minor trauma	0	0
Highest eosinophil count (cells/ml)	0	0
Characteristic face	2	2
Midline anomaly	0	0
Newborn rash	0	0
Eczema (worst stage)	1	1
Upper respiratory infections per year	4 (otitis media)	4 (otitis media)
Candidiasis	1	0
Other serious infections	4	4
Fatal infection	0	0
Hyperextensibility	4	4
Lymphoma	0	0
Increased nasal width	0	0
High palate	0	0
Young-age correction	3	3
TOTAL SCORE	31	34

period and persisting through the teenage years, with the development of cold abscesses and recurrent pulmonary infections usually starting in early childhood. Characteristic facial features and other skeletal abnormalities (i.e., scoliosis and osteopenia) typically

manifest during adolescence.¹⁰ Craniosynostosis can be present, but is not a specific feature, as it can also manifest in several syndromes.²⁴ The premature closure of cranial sutures should prompt awareness of the potential presence of systemic involvement. Indeed, craniosynostosis had been a known association with hyper-IgE syndrome since 1985, when the molecular causes of HIES were unknown.¹⁶ While each event in the case was not unique to children, the constellation of events in identical siblings should have prompted immune evaluation earlier. An AD-HIES should be suspected, especially when craniosynostosis is accompanied by recurrent ear, respiratory and skin infections. In addition, now, STAT3 gene is generally included in the panel of genes analyzed in cases of craniosynostosis (such as PanelApp <https://panelapp.genomicsengland.co.uk/panels/168/>). This case report should highlight that AD-HIES can present with craniosynostosis in early infancy. This is very relevant because AD-HIES can represent a challenging diagnosis in the first months of life when IgE can still not be extremely elevated. Recent data have shown that early prophylaxis in AD-HIES leads to improved lung function and decreased structural lung disease in patients. Available treatments include immunoglobulin substitution and antimicrobial prophylaxis, and also HSCT, although this later treatment has no impact on the musculoskeletal aspects of the syndrome.

AUTHOR CONTRIBUTIONS

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craniosynostosis, hyper-IgE syndrome, Job's syndrome

CONFLICT OF INTEREST STATEMENT

The authors have declared no conflicts of interest.

ETHICS APPROVAL

Informed consent for the publication of this letter was obtained from the parents.

PEER REVIEW

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