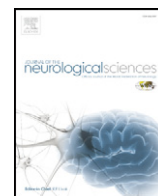




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Community acquired *Staphylococcus aureus* meningitis and cerebral abscesses in a patient with a Hyper-IgE and a Dubowitz-like syndrome

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ABSTRACT

The Hyper-IgE syndrome (HIES) is a rare primary immunodeficiency which recently has been associated with heterozygous dominant-negative mutations in the signal transducer and activator of transcription 3 (STAT3). Although HIES is characterized by recurrent staphylococcal infections, the microbial invasion of the central nervous system (CNS) is definitively uncommon. We here report on *Staphylococcus aureus* meningitis and cerebral abscesses acquired in the community in a 31-year-old female patient with a *de novo* heterozygous mutation of STAT3 and a Dubowitz-like syndrome characterized by growth retardation, microcephaly and eczema. The patient presented with a relative paucity of clinical symptoms despite severe cerebrospinal fluid pathology and multiple cerebral abscesses. Antimicrobial as well as treatment with intravenous immunoglobulin was well tolerated and led to a slow recovery over a 6 months period. Our observation adds community acquired *S. aureus* meningitis to the list of life-threatening infections in STAT3-deficient HIES and should also raise awareness for the unusual clinical presentation of severe neuroinfection in this syndrome. Whether the association of HIES with Dubowitz-like syndrome was purely coincidental, possibly supportive of the CNS infection, or suggests a genetic overlap of these syndromes, awaits clarification.

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1. Introduction

Staphylococcus aureus meningitis is rare but has devastating clinical consequences and elevated mortality rates, especially if it is acquired in the community [1,2]. The Hyper-Immunoglobulin E syndromes are rare primary immunodeficiencies characterized by elevated serum IgE, dermatitis and recurrent skin and lung infections [3–6]. These infections usually start in early childhood and *S. aureus* is most frequently cultured from various specimens [3,4]. A remarkable clinical feature of HIES is that infections are not accompanied by a normal intensity of pain or inflammation. In 2007 mutations in signal transducer and activator of transcription 3 (STAT3) were identified to be a cause of the autosomal dominant HIES and most sporadic cases [7], and recently diagnostic guidelines for STAT3-deficient HIES were established [6]. Here we report on community acquired *S. aureus* meningitis in an adult patient with STAT3-deficient HIES to raise awareness for this disorder since the recognition of the obviously unusual clinical presentation and course of CNS infections in HIES may

aid early diagnosis and management in similar cases. Interestingly our patient also showed features of Dubowitz syndrome which is a different genetic disorder with autosomal recessive inheritance [8].

2. Case report

A 31-year-old unconscious female was admitted to the emergency department. She had a 2-week history of fatigue. Headache or fever had not been reported. On admission she scored 8 points (E1, M5, V2) on the Glasgow coma scale (GCS). Neurological examination revealed neck stiffness and a mild right hemiparesis. Body temperature was 36.5 °C, pulse rate 110/min and blood pressure 120/85 mmHg. An unusual facial appearance, severe Onychomycosis, multiple scars on the thumb and the extremities, dysmorphic disorders of both hands, amputation of her right fifth finger and a short stature (length 140 cm, body weight 45 kg) were remarkable on physical examination. Routine laboratory testing was normal except for a mild anemia. Contrast enhanced CT of the brain disclosed an acute hydrocephalus, and multiple ring-enhancing lesions (Fig. 1A). There was no evidence of hydrocephalus on imaging performed 18 months earlier and the decision to urgently place an external ventricular drainage (EVD) was made. Analysis of the cerebrospinal fluid (CSF) showed neutrophilic

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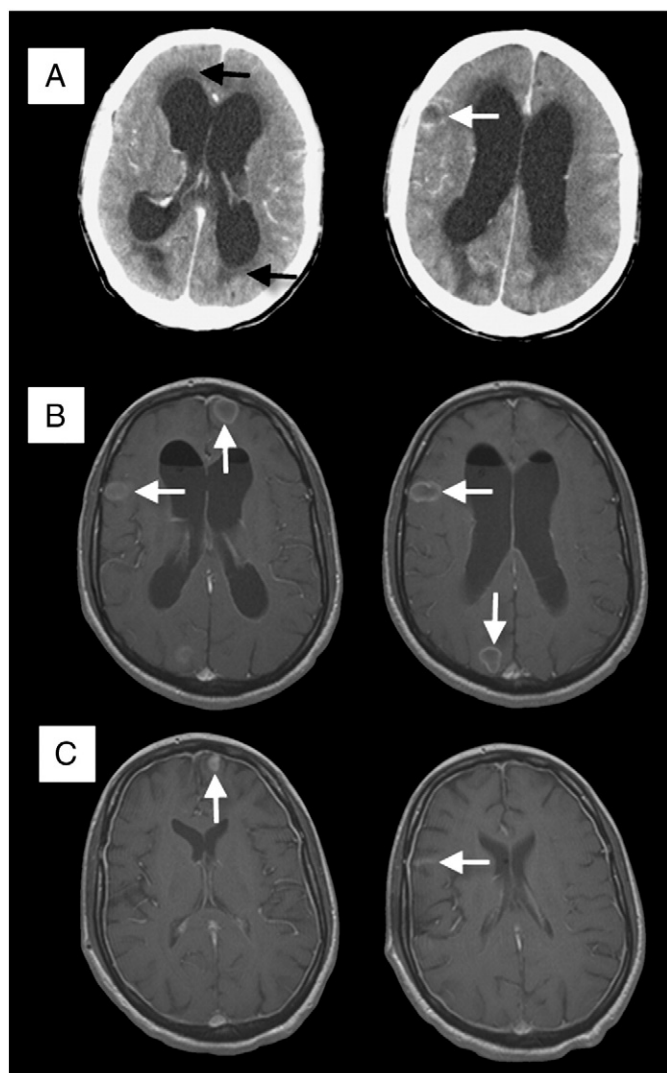


Fig. 1. Contrast enhanced CT of the brain at admission shows a significant dilatation of the ventricular system and signs of transependymal transudation (black arrows) consistent with an acute hydrocephalus as well as a ring enhancing lesion (white arrow) consistent with cerebral abscess (A). Contrast enhanced T1 weighted magnetic resonance images of the brain performed 14 days later shows multiple cerebral abscesses in both hemispheres (arrows) and beginning regression of the acute hydrocephalus subsequent EVD placement (B). Corresponding magnetic resonance images following therapy 4 months later (C) illustrate an obviously declining appearance of the abscesses (arrows) with residual contrast enhancement and normal size of the ventricular system subsequent ventricular shunting.

granulocytic pleocytosis (cell count 323/mm³; total protein 280 mg/dl; lactate 5.6 mmol/l; glucose 6 mg/dl) and the CSF/blood glucose ratio was 0.09. Methicillin susceptible *S. aureus* (MSSA) was cultured from the CSF and the diagnosis of community acquired MSSA meningitis was established. Contrast enhanced MRI of the brain performed 14 days later illustrated beginning regression of the acute hydrocephalus that was obviously due to disturbed resorption caused by the meningitis and confirmed the presence of multiple cerebral abscesses (Fig. 1B). Transoesophageal echocardiography revealed no evidence of endocarditis. Chest X-ray was normal but a contrast enhanced CT of the thorax depicted multiple small pulmonary abscesses. No further pathogens could be cultured from pulmonary specimens, repeated CSF, the blood or from the ventricular catheter. Additional laboratory testing showed excessively elevated total Serum IgE (10300 IU/ml; normal range 0–100 IU/ml) but no other abnormal findings despite of an extended search for autoimmune, metabolic or endocrine disease. Further evaluation revealed several additional abnormalities suggestive of the presence of a multisystem disorder in our patient (Table 1 and Fig. 2).

Table 1
Clinical features of HIES and Dubowitz syndrome.

Clinical finding	Patient	HIES	Dubowitz
Craniofacial abnormalities			
Microcephaly (circumference 52 cm)	+	–	+
High prominent forehead	+	+	+
Facial hemihypertrophy	+	+	–
Low set dysplastic ears	+	–	+
Mild prognathism	+	+	–
Thin vermilion boarder of the upper lip	+	–	+
Skeletal abnormalities			
Short stature (140 cm)	+	–	+
Scoliosis (12°)	+	+	+
Osteoporosis (lumbar)	+	+	–
Pathologic bone fracture (rip)	+	+	–
Hip dysplasia	+	–	+
Clinodacty of the 5th finger	+	–	+
Others			
Eczema (severe within the 1st month; and recurrent episodes)	+	+	+
Rough skin	+	+	+
Cathedral palate	+	+	+
Retained primary teeth	+	+	–
Hernia inguinalis (operated in the 5th month)	+	–	+
Characteristic behaviour patterns	+	–	+
Psychomotor retardation	+	–	+
High-pitched voice	+	–	+

2.1. Medical history and diagnosis

A detailed medical history was obtained by reviewing all available medical records of the patient. She was the first child of her parents from a rural area. Following uneventful pregnancy and delivery, she was born at term. Birth weight was 2600 g; length was 47 cm. During the first month severe eczema required hospitalization. Subsequently growth retardation and mild psychomotor delay were increasingly observed. Since the age of one year a history of recurrent infections was recorded and *S. aureus* was typically cultured from various specimens. At the age of 31 years the Hyper-IgE-score according to Grimbacher et al. was 77 points [9], but only when the patient presented with this episode of meningitis and cerebral abscesses a clinical diagnosis of the possible HIES [6] in coexistence with a Dubowitz-like syndrome was established. Characteristic features of HIES and Dubowitz syndrome that partly overlap in the patient are listed in Table 1.

2.2. Clinical course and treatment

After the EVD was placed consciousness significantly improved (GCS 15) and there was no hemiparesis. Antimicrobial treatment with ceftriaxone, fosfomycin and metronidazole was administered. Remarkably, no elevations of C-reactive protein, leukocytes or body temperature were noted. As the diagnosis of the possible HIES [6] was suggested treatment with IVIG was started. After the initial application of IVIG (0.4 g/kg body weight per day for 5 days), C-reactive protein increased from 0.1 mg/l to 32.8 mg/l (normal range 0.1–8 mg/l) the patient developed fever up to 38.5 °C for the first time and total IgE decreased from 10300 IU/ml to 7230 IU/ml. Raising the EVD to a more positive height led to prompt neurologic decline of the patient. The CSF findings slowly normalized and a ventriculoperitoneal shunt was inserted 7 weeks after admission. Treatment with IVIG was continued at a 4-week interval for half a year for a cumulative dose of 540 g. The patient initially continued to improve clinically and with regard to “surrogate disease markers” on the MRI (Fig. 1B,C). Antimicrobial treatment with Ceftriaxone was continued for 73 days and subsequently oral Cefalexin was established. Our patient was able to walk again and no severe infections were recorded within 24 months of follow up.



Fig. 2. Note distinct features of HIES and a Dubowitz-like syndrome: Prominent forehead, right facial hemihypertrophy, mild prognatism (A) and a short stature (B). Pronounced candidiasis of the fingernails, amputation of her right fifth finger, severe malposition of the fingers and marked dysmorphic disorders of both hands (C) most likely following recurrent infections.

2.3. Functional testing, genetic analysis and immunological findings

To assess functionality of *STAT3* signaling, peripheral blood mononuclear cells of the patient and healthy controls were stimulated with lipopolysaccharide (LPS), co-stimulated with LPS and IL10 or left untreated; after 18 h incubation TNF α concentrations in the supernatants were measured by ELISA [6]. In contrast to healthy controls, patient's cells showed significantly impaired IL10-mediated suppression of TNF α release, indicating a failure of *STAT3* signaling. Subsequent sequencing *STAT3* revealed a heterozygous missense mutation in exon 13 leading to the amino acid exchange R382W in the patient whereas the parents and brother showed a wild type sequence.

The search for a Dubowitz syndrome causing gene was inconclusive. Cytogenetic analysis and microarray CGH analysis (Agilent 244k Oligonucleotide array) revealed a normal result. Affymetrix Genome-Wide Human SNP Array 6.0 analysis of the patient and her parents was performed. Three genomic segments larger than 3–5 Mb, which are homozygous in the patient, were identified. Consanguinity of the parents could not be ruled out definitively. There was no clinical evidence of HIES and functional as well as genetic testing for *STAT3* deficiency was negative in the parents and brother of the patient.

3. Discussion

Staphylococcus aureus accounts for less than 3% of bacterial meningitis acquired in the community [1], however it is associated

with a mortality rate of 50%. Hydrocephalus or cerebral abscesses are very rare complications of the disease that occur in less than 1% [1,2]. *Staphylococcus aureus* is the most common pathogen in the HIES [3,4]. Affected patients usually present with recurrent staphylococcal skin infections and pyogenic pneumonias, but microbial CNS invasion is rare. We herein reported for the first time on community acquired *S. aureus* meningitis in an adult patient with a *de novo* mutation of *STAT3* and a Dubowitz-like syndrome.

MSSA meningitis had obviously been acquired in the community in our patient as no contact to hospitals had been recorded in the months prior to admission. Distant foci of infection outside the CNS are frequently found in patients with community acquired *S. aureus* meningitis and were present in 89% on admission in a recent study [2]. Indeed, extensive evaluation of our patient revealed pulmonary abscesses that were clinically “cold,” which is not unusual in HIES where a relative lack of symptoms compared to the extent of pulmonary disease or dermal pathology is a well recognized feature [6]. However, the paucity of clinical symptoms in severe human neuroinfection has not yet been described with this syndrome, most likely due to the rarity of this condition. In our patient meningitis developed over at least 2 weeks and she was primarily fatigued before she became obtunded due to hydrocephalus. In this context, the coincidence of two especially rare complications of community acquired bacterial meningitis such as hydrocephalus and cerebral abscesses is also remarkable.

Several immune modulators have been clinically unsuccessful in the management of HIES. At least two case reports used moderate- or high-dose IVIG with good [10] or partial [11] success. IVIG can therefore not generally be recommended for all patients with similar disorders as encountered in our patient. The use of IVIG, however, may be reasonable to consider, as integrity of antibody formation, especially against encapsulated organisms, appears to be impaired in HIES. IVIG may also influence the IgE-levels due to an increased Ig-catabolism or IgE-neutralization via an anti-idiotypic network. We observed not only a significant decline of total IgE after the application of IVIG, but it is also remarkable that clinical and laboratory markers of infection increased and subsequently the patient significantly improved, suggesting a possible beneficial effect of IVIG with an increased ability to control invading microorganisms.

The Dubowitz syndrome, defined as a condition of pre- and postnatal growth retardation, microcephaly and eczema, is a rare disease with autosomal recessive inheritance [8]. The genetic basis of the syndrome, however, remains widely unclear. Moreover, frequent infections have been reported in connection with the Dubowitz syndrome [8]. An association of HIES and the Dubowitz syndrome has been suggested previously but in this context mutations of *STAT3* have not been addressed [12,13]. Our case strengthens this observation. However, it still remains unclear if association of *STAT3*-deficient HIES with a Dubowitz-like syndrome suggests some genetic linkage or simply comes from the fact that the coexistence of both disorders promoted the life-threatening invasion of the CNS by MSSA in our patient.

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