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Case Report
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Hyper-Immune-Globulin E Syndrome and Cryptococcal Meningitis Leading to a Fatal Outcome in a Young Woman: A Rare and Lethal Combination

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Abstract

Background: The very rare syndrome, hyper-immunoglobulin E, also known as Job or Buckley syndrome, is characterized by multiple skeletal and cutaneous disorders, but also can present with potentially fatal infectious diseases rarely seen and not always considered. With HIV positive patients, or patients on immunosuppressive agents, for example, Cryptococcal meningitis is often considered for any neurologic presentation; however in patients not appreciated to be immunocompromised consideration of that disorder is frequently delayed with worsening mortality. The Hyper-IgE syndrome has not, to our knowledge, been presented in the emergency medicine literature.

Case Report: We present the case of a young woman with this syndrome who presented with neurologic symptoms and in whom the diagnosis of Cryptococcal meningitis was only made after repeated emergency department visits and a several day hospital admission, and who succumbed.

Literature showing worse prognosis for CM in non-HIV patients is reviewed, as well as an analysis of cognitive biases in decision making. We believe the introduction of this fortunately exceedingly rare condition of immunocompromised, and review of the too often undetected presentation of CM in non-HIV patients will be of value.

Keywords: Hyper IgE syndrome; Immunocompromised; Cryptococcal meningitis; Cognitive bias; Rare disease

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Introduction

Hyper-immunoglobulin E syndrome, "HIES", also known as Job syndrome, Buckley syndrome and STAT3 deficiency [1], is a condition characterized by chronic eczema, distinctive facial features, retention of primary teeth, skeletal abnormalities leading both to fractures and to scoliosis. The syndrome predisposes to recurrent and chronic staphylococcal skin infections and abscesses, as well as recurrent pulmonary infections leading to pulmonary cysts and pneumatoceles [2]. The syndrome is a primary immunodeficiency syndrome which patients also share common facial, skeletal and cutaneous characteristics [1,3]. Most cases are transmitted in an Autosomal Dominant inheritance pattern (AD), but it has been found to be sporadic as well as showing an autosomal recessive inheritance pattern in some patients. Seventy percent of AD-HIES cases are associated with a mutation in the *STAT3* gene [4]. This result in abnormalities in signal transduction causes a number of immunologic alterations which lead to an increased risk to bacterial and fungal infections. These infections can be sinopulmonary, cutaneous, and in rare cases gastrointestinal or CNS.

The syndrome is fortunately quite rare, presenting once in a million live births [5]. Presentations are therefore not commonly seen in the emergency department. Descriptions and cases do not, in fact, appear in any text-book of emergency medicine or emergency medicine journals we have found. Reviews have primarily been found in NIH sources [6] and Journals of Immunology, Allergy, Dermatology [7,8]. The consequent unfamiliarity with this syndrome and its dangers can have devastating consequences, as fatal infections occur. The average life span of a patient with HIES is 27 years, and the average age of fatal infections is 29 years, although some patients have been known to live into their fifties. This increases the need to be cognizant of the condition and its potentially deadly consequences.

The timely recognition of potentially lethal infections in this rare disorder is further delayed because HIES predisposes patients to subacute, indolent and initially subtle but potentially lethal

infections. These include invasive mycoses. Odio and others, in a letter to the editor of the Journal of Allergy and Clinical Immunology [7], presented 5 cases of patients with HIES who were infected with endemic mycoses. As far as we have found, three patients have previously been reported in the literature with HIES and Cryptococcal Neoformans meningitis [7,8].

We report here a case of a young woman having Hyper-immunoglobulin E syndrome, with a history of chronic epilepsy and migraine headaches who presented twice to the Emergency Department with headaches, seizures and anxiety. She was not initially admitted, and when admitted was not considered to have CNS infection. We believe the case worthy of consideration to raise consideration both for this very rare underlying condition and for the presentation in unusual circumstances of a subtle but dangerous CNS infection.

Case Presentation

A 26-year-old woman with a history of a prior resection of a frontal cavernoma and a history of seizures on Vimpat presented with one day of frontal headaches and with two weeks increased seizure frequency. She had no fever, chills, stiff neck, nausea or vomiting, or neurologic deficits, and a complete neurologic exam found no focal abnormalities. CT revealed focal encephalomalacia underlying the old craniotomy. Laboratory evaluation was normal. The patient was discussed with her neurologist who recommended medical management of her headache, and she felt improved after an injection of an antiemetic. She was discharged to follow up with her neurologist.

The patient returned the next day with complaints of tingling and numbness which she associated with anxiety. She was reported to be under emotional stress, and denied fever, chills or focal weakness. She was a febrile, her neck was supple with full range of motion, her neurologic exam was normal, as was laboratory evaluation including a repeat CT scan. She appeared "anxious and ill", however, and after discussion with her neurologist, was recommended to stay for video-EEG and neurological evaluation. After discussion between herself and her family the patient decided against staying under observation in hospital and elected to leave against medical advice. She was advised to contact her neurologist.

Reportedly the patient continued to have headaches and was placed nine days later on Verapamil for headaches.

She returned the next week, now 11 days after her initial visit to the ED with complaints by the family of her having a "blank stare" and not responding appropriately to voice. She appeared to be slow to respond to questions. She was considered to appear post-ictal and was placed in hospital for Video-Electroencephalographic Monitoring (VEEG). At this time, her past medical history was documented to include Hyper-IGE syndrome and seizures. She was noted to be chronically ill appearing and awake but minimally responsive to speech, with no focal neurological signs, and an otherwise unremarkable physical exam.

The patient remained confused for the next twenty four hours at which time she was noted to have a fever of 101. Blood cultures were drawn. A chest X-ray showed "pleural parenchymal disease" and antibiotics were started for possible pneumonia. At that time, she was noted to be awake, alert, oriented, and her neck noted to be supple.

Over the next twenty-four hours she remained intermittently lethargic and confused. She was placed on intravenous fluids and antibiotics and continuously monitored. Video EEG showed moderate diffuse slowing, but no epileptiform abnormalities. The patient remained drowsy but easily arousable. Over the next day she became "non-verbal". An MRI was recommended. A lumbar puncture was considered, but it was decided and documented by the clinical team to defer because the patient's lethargy appeared to her clinicians to be improving.

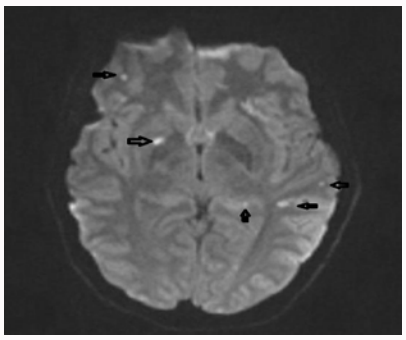

Figure 1: MRI brain on this DWI sequence, multiple small bilateral hemispheric infarcts is noted (arrows).

The MRI of the brain was performed and showed multiple small bilateral supratentorial and pontine infarcts suggestive of an embolic source see Figure 1.

Lumbar puncture and echocardiogram were recommended. Prompted by the concern for micro-embolization, a CT angiogram of the head and neck was also performed. It revealed no evidence for a flow-limiting stenosis or vasospasm. Small density foci in the cerebrum corresponded to the multifocal infarcts read on the prior MRI. It was noted that the relative loss of sulcation of the brain, stable, might be related to a leptomeningeal process given the conspicuity of sulcal FLAIR signal abnormality on the prior MRI.

Blood cultures then returned positive for a yeast species, which was subsequently identified as *Cryptococcus Neoformans*. She was started at that time on intravenous Caspofungin. A respiratory pathogen panel was negative. A transesophageal echo was recommended.

At that point an allergy-immunology consultation was obtained and the diagnosis of Hyper-IgE syndrome was further elucidated. A serum IgE was obtained, and she was shown to have a level of IgE of 2285 (n<233). She was noted to have a multiple year history of recurrent pneumonias, a prior pneumatocele, prior otitis, a prior psoas abscess and severe eczema. Further Immunologic work up was recommended. Rheumatology consultation was also obtained. The impression was there were no signs of a co-existent autoimmune inflammatory disorder.

The following day the patient was scheduled for a lumbar puncture under interventional radiology. She seemed more responsive, more interactive and spoke with her mother. However, she was noted to have increasing hypoxia, and was considered to have aspiration and possible septic shock. Based on clinical worsening, Amphotericin was added to her anti-fungal coverage. She appeared increasingly dyspneic, was placed on non-invasive ventilation, and was admitted to the ICU.

Her lumbar puncture results included WBC 2, RBC 18, glucose <20 and a very high Cryptococcal titer. A diagnosis of Cryptococcal

meningitis was made. Antifungal agents were broadened to include Flucytosine.

Her mental status continued to deteriorate, and she was intubated.

Another head CT was obtained at that time and revealed significantly worsening diffuse brain swelling, with complete effacement of the suprasellar cistern and downward central herniation, new caudal tonsillar herniation, and pronounced effacement of the prepontine cistern. There was new significant loss of grey white, suggestive of diffuse cerebral edema.

Mannitol and hypertonic saline were given, however no improvement was noted. She was judged to have no brainstem function and no chance of survival.

The patient was terminally extubated and pronounced dead on hospital day 8.

Discussion

While Cryptococcal Meningitis has been traditionally recognized among HIV/AIDS patients [9] and neurologic symptoms in AIDS patients generally lead clinicians to evaluate CSF of a patient with a headache [10], it is not as often expected, but also seen in non-HIV patients [11]. Most cases, worldwide still occur in HIV AIDs, with 220,000 cases per year, mostly in Africa, and a very high, 70% mortality. In China however, for example, the majority of patients who present with cryptococcal meningitis are reported not to be HIV positive, but rather immunocompromised from other sources, including organ transplantation [12]. Their report cites another article as source for one million cases actually in patients with HIV [13].

They see a high, nearly 70% mortality. These authors cite a "hidden onset and slow course" for one reason of the high mortality.

For the HIV-seronegative patient [14] with *Cryptococcus neoformans* infection, often an underlying risk factor such as glucocorticoid use, hematologic malignancies or a history of solid organ transplantation and the use of immunosuppressive agents. Recently an apparently immunocompetent patient was reported to have cryptococcal meningitis [15].

Reports have also shown a longer interval from presentation to diagnosis, especially in non-HIV patients. A 14-year study at Duke University Medical Center shows the duration of symptoms in HIV-seronegative non-organ transplant group is 44 days compared to 19 days in HIV positive group, and 24 days in transplant patient group [16]. Non-HIV patients are diagnosed later, possibly because the disorder is not as readily anticipated. Another study at University of Alabama at Birmingham shows a significant difference between the mean time to diagnosis among three groups [17]. The mean time to diagnosis among HIV-seronegative and non-organ transplant group is 68 days, which is longer in comparison to time to diagnosis of 22 days in HIV positive patient and 26 days in organ transplant recipient [9].

Symptoms of cryptococcal meningitis include an insidious onset, waxing and waning of the course, and non-specific findings, but also include headache, nausea, vomiting, ultimately disturbances of consciousness, hemiplegia, ataxia and seizures, although infrequently typical signs of meningeal irritation can be seen. Due to the insidious onset, average time from symptom onset to diagnosis as 30 days [18], which was compatible with the timeline in this case, considering that the patient had a vague increase in the frequency of her seizures and headache starting two weeks prior to her initial presentation, and about three before her hospitalization. On occasion the presentation can be so vague as to suggest psychiatric disease, which echoes our patient's chief complaint of anxiety and stress on her second visit [19].

Prolonged interval from presentation to diagnosis, such as is more commonly seen in the non-HIV presentation [12,13], can increase the chances of a fatal outcome such as occurred in our case study. In addition, compared to patients with HIV, HIV-negative individuals with cryptococcal meningitis are at increased risk of having cryptococcal parenchymal lesions, inflammation and thus higher risk of herniation [20-22].

One case series of four cryptococcal meningitis cases cites cognitive bias and knowledge deficits as reasons for diagnostic error. As front-line providers, emergency medicine physicians can easily fall prey to "reasoning shortcuts" which include, but are not limited to, failure to recognize immunosuppression while assuming the common diagnosis is more likely. We believe the rarity of HIES syndrome and the lack of reports in emergency medicine literature may have contributed to an initial unfamiliarity with this being a syndrome of immunosuppression. Other reported cognitive biases include anchoring in the context of finding an alternative diagnostic answer. This may have occurred when a post-ictal state in a seizure patient was thought to account for a period of confusion. Such anchoring can result in closing prematurely one's differential diagnosis for the case, especially when symptoms improve with medical management and framing where diagnostic conclusions are biased by the manner in which objective information had been presented [23].

Our patient was initially started on fluconazole, but when the diagnosis was made her regimen was expanded to include amphotericin and flucytosine [24]. Induction therapy [25] can be given for four weeks in patients with meningoencephalitis without neurologic complications. However for patients with neurological deficits this can be expanded to a six week course. Liposomal amphotericin [26] can be substituted if induction therapy is extended to prevent complications. After six weeks, consolidation treatment daily follows for eight weeks, and this is followed by maintenance therapy, or suppression, for a year or longer.

We believe that for our patient the combination of a rare and unfamiliar congenital disease of immune deficiency predisposed our patient to a slow, insidious but ultimately fatal illness which presented with headache and apparent increased frequency of her seizures. Because our patient was known to chronically suffer with both symptoms from other causes, meningitis was not considered on initial and early evaluations. Owing to the combination of the rarity of the disease, the existence of other similar presenting complaints in the patient's history, and the gradual indolence of presentation of this disease, the ultimate diagnosis was not made until positive blood cultures prompted antifungal therapy and lumbar puncture.

We write this case in the hope that a raised awareness of this rare congenital condition, hitherto unreported in the emergency medicine literature the increased consideration of the potential for such causes of slowly progressive chronic neurologic conditions and chronic meningoencephalitis may have the potential to improve the possibilities of early recognition of this presentation for other, albeit very rare, patients.

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