

DIVERSE NEUROLOGICAL MANIFESTATION OF HYPERIMMUNOGLOBULIN-E SYNDROME: A CASE SERIES

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ABSTRACT

Hyper-immunoglobulin E (IgE) is a disorder of immune system characterized by assemblage of symptoms including recurrent skin and pulmonary infections, skeletal anomalies and elevated serum IgE (>2000 IU/ml). More recently, apart from the typical features, neurological manifestations have also been described including central nervous system infections, facial nerve palsy and demyelinating disorders. Here we describe three patients with hyper IgE syndrome having diverse neurological manifestation varying from CNS infection to basal ganglia stroke and progressive leukoencephalopathy.

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hyper IgE syndrome presenting at variable ages with stroke, encephalopathy and ataxia respectively.

CASE SERIES

CASE I

A 9 years old girl was born to consanguineous parents, 3rd in order of four siblings, vaccinated and had achieved age-appropriate milestones. She presented to neurology department with complains of abnormal right sided choreiform movements for last 6 months. These movements, initially subtle, had progressed overtime to the development of right sided body weakness. There were also associated academic difficulties, progressive cognitive decline and loss of self-care. The motor deficits continued to progress and evolved into generalized body weakness over a period of 4 months, making the child completely bed bound. With the advancing disease, she became encephalopathic. On reviewing her previous history, she had h/o skin rash since 6 months of age with recurrent sino pulmonary infections requiring multiple hospital admissions & outpatient visits but without a definite diagnosis. Examination showed an emaciated girl with height and weight parameters below 3rd centiles, having grade III clubbing, thin sparse hair, multiple eczematous lesions over the body and contractures at knees and ankles. Neurological examination showed GCS 9/15,

INTRODUCTION

Hyper IgE, or commonly termed as Job syndrome, is an inborn error of immune system which classically manifests with recurrent eczematous rash, frequent *staphylococcal* cutaneous and sino-pulmonary infections and raised IgE levels.¹ It is still considered to be a rare disorder with incidence of less than 1/100,000 without any ethnic or gender predilection.² The inheritance is either autosomal dominant or recessive depending upon different genetic variants.³ Over the past decade, with the advent of research and genetics, many add on clinical features have emerged including cranio-facial and dentition anomalies, cardiac and vascular defects and neurological manifestations. Due to the rarity, there have been mainly case reports describing neurological manifestations ranging from infectious events including herpetic and fungal infection to non-infectious thromboembolic, para-infectious demyelinating events and recurrent facial nerve palsy.^{4,5} Through this case series, we describe three patients with

generalized hypertonia and hyperreflexia, with right side power 1/5 while left side 3/5 and bilateral extensor planter reflex. She had intact cranial nerves with a normal fundus examination. Chest had bilateral coarse crepitation with areas of bronchial breathing. Rest of the systemic examination was within normal limits. In the emergency room, her CT brain showed hypodense lesion in the left basal ganglia. She was transferred to neurology high dependency unit for work up of stroke. Considering previous long history of skin rashes and pulmonary infections with a regressing neurological course complicated with stroke, differentials of immunodeficiency vs Biotinidase deficiency/metabolic strokes were considered and work up extended.

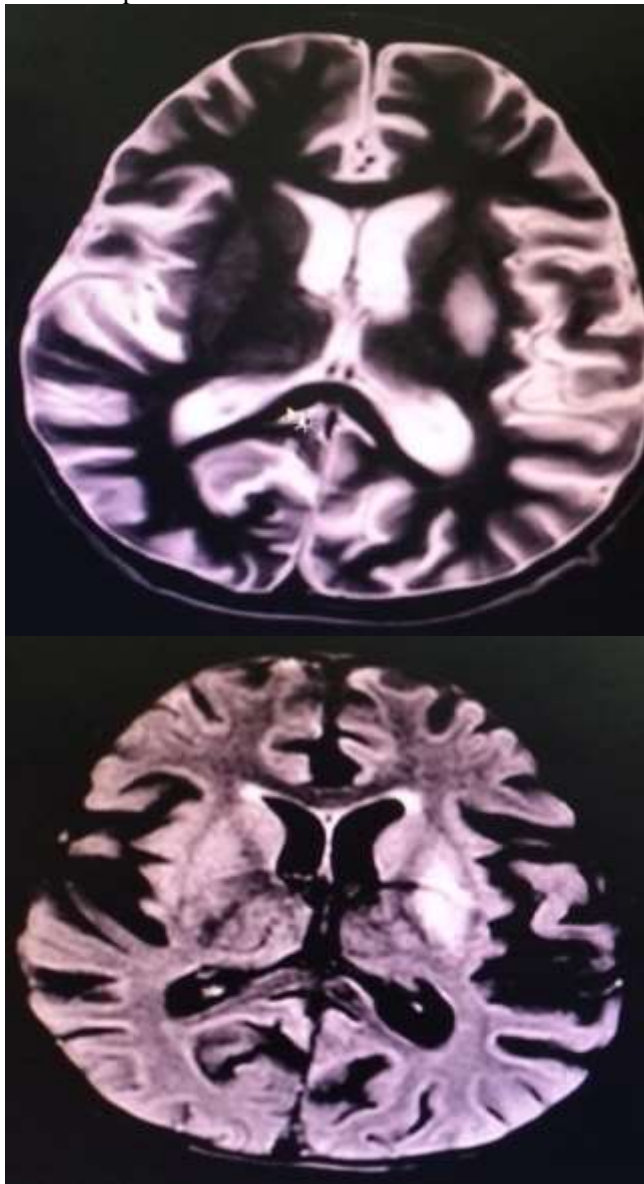


Figure 1: MRI brain t2w and flair images showing left basal ganglia hyperintensity with dilated ventricular and extra-ventricular spaces

MRI brain showed 26x14mm sized infarct in the left basal ganglia with dilated ventricular and extra-ventricular spaces consistent with cortical atrophy (FIGURE 1). For the work up of stroke, her cardiac screen including electrocardiography and echocardiogram was normal. Protein C, S, anti-thrombin III, autoimmune profile was unremarkable. Hemogram showed anemia, flow cytometry showed low total lymphocyte count. Her renal, liver and bone profiles were within normal limits. Anion gap, ammonia, lactate levels and urinary organic acids were normal. Her HIV, COVID and tuberculosis screen was also negative. Blood cultures showed no growth. Immunoglobulin levels showed normal IgA, IgG and IgM but her IgE levels came out to be markedly increased (9363 IU/ml) fulfilling the criteria for hyper IgE syndrome. She was managed with aspirin and neuroprotective measures alongside the treatment of skin and pulmonary infection

Specimen: Peripheral Blood
Panel: 6 color TBNK
WBC count: 10.2 x10³/ul.

Results

Parameter	Percent %	Abs count
CD3 + cells	44.6	289 ↓↓
CD3 + CD8 + cells	25.1	162 ↓
CD3 + CD4 + cells	14.8	95
CD3 + CD4 + CD8 + cells	0.5	03
CD16 + CD56 + cells	12.6	81 ↓
CD19 + cells	38.0	251 ↓
CD4/CD8 ratio		4.7
%T- sum = 4.7		

Comments:

Total lymphocyte count is low in peripheral blood. Correlate results accordingly.

Figure 2: Flow cytometry showing low total lymphocyte count



Figure 3: CXR showing left lower zone consolidation

CASE II

8 years old girl, born to non-consanguineous marriage, 3rd child with no significant family history of note. She was previously diagnosed with hyper IgE syndrome on basis of recurrent skin infections including erythematous pustules since age of 1.5 months, frequent chest infection and high IgE levels (14680 IU/ml). For these complaints, she had previously been hospitalized multiple times and received antibiotics and supportive treatment. 2 months back, she presented with complains of fever and headache for 15 days, generalized tonic clonic seizures and altered state of consciousness for 2 days. Examination showed GCS 8/15, positive signs of meningeal irritation, generalized hypertonia and hyperreflexia with upgoing planter reflex, bilateral ptosis and right abducens nerve palsy. Moreover, she had multiple eczematous lesions and pustules over her body, hyperextensible joints and retained primary dentition. There were signs of respiratory distress with chest full of crepitations. An urgent CT brain was done that showed multiple small hypodense areas scattered throughout the brain parenchyma with normal ventricular system. Lumbar puncture was performed showing lymphocytic pleocytosis, raised proteins and positive gene Xpert. CXR showed areas of consolidation bilaterally. MRI brain showed T1W contrast enhancing and T2W hypointense lesions consistent with tuberculomas. Child was immediately started on anti-tuberculous therapy along with steroids but the response was unsatisfactory and she continued to deteriorate neurologically with worsening in her GCS, development of decerebrate posturing and later ATT induced hepatitis. She was switched to second line ATT along with continuation of neuroprotective measures but the course was downhill with severe respiratory infection, hemodynamic instability and multi-organ dysfunction that led to the demise of the patient.



Figure 4: MRI brain sagittal t1w showing multiple contrast enhancing lesions in cerebral cortex and brainstem



Figure 5: MRI brain flair image showing hyperintense signals in the temporo-occipital cortex and brainstem

CASE III:

4 years old boy, 2nd in order of 3 siblings, born to consanguineous parents, unvaccinated and developmentally age appropriate till 3.2 years of age. He had history of recurrent fever since 3.2 years of age, high grade, documented up to 102-103 F without any vomiting, diarrheal illness, abdominal pain, flu like symptoms, cough, rash, arthralgias, seizures or urinary complaints. For this, he had required hospitalization and all work up for fever came negative. After 2 months of this recurring fever, he developed walking difficulty with frequent falls accompanied with tremulous body movements requiring assisted walk and help in holding spoons and toys. There was associated hyperactivity with limited on seat time, excessive talking, fearfulness and poor sleep hygiene with daily sleep arousals. The past medical history was insignificant for any skin or pulmonary infections or any significant family history. Examination showed a conscious alert boy with excessive talking, having slightly blond hair and fair skin. Neurological examination showed ataxic gait, hand tremors and hypotonia with normally elicitable reflexes and down going planters. There was no nystagmus, cranial nerve examination was also normal. Systemic examination was within normal limits.

He was investigated for cerebellar pathology in lieu of cerebellar signs but his MRI brain showed symmetrical white matter hyperintensities as shown in FIGURE 6 and 7. Considering mitochondrial disorder, his lactate and magnetic resonance spectroscopy was also done that came normal.



Figure 6: MRI brain t2w images showing bilateral symmetrical periventricular white matter hyperintensities

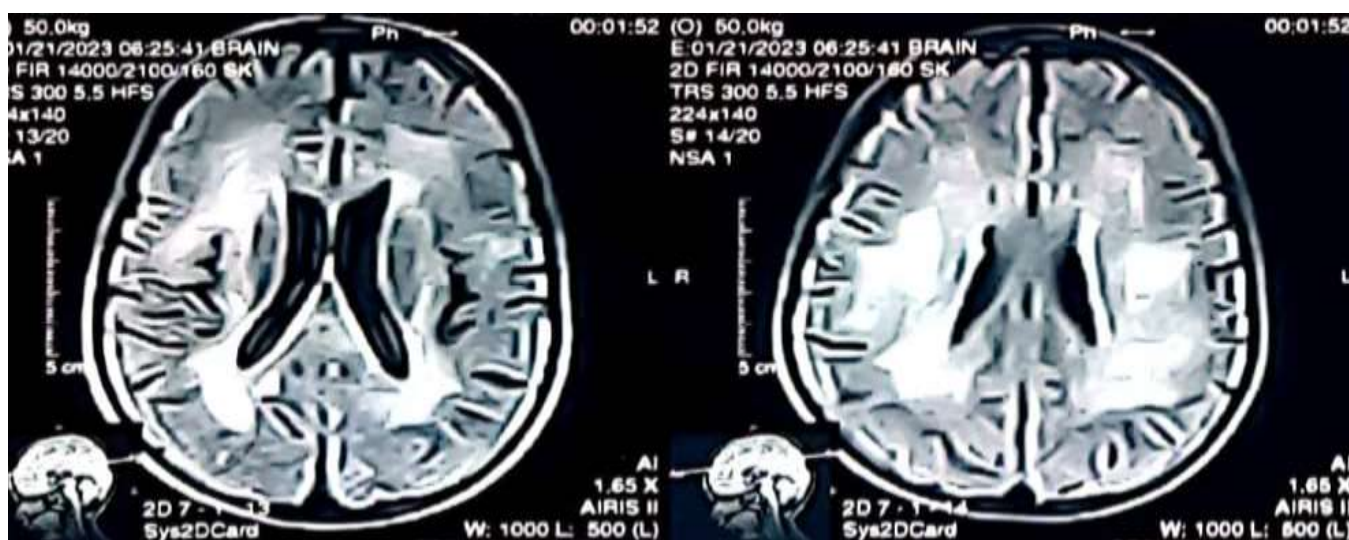


Figure 7: MRI brain flair image showing bilateral symmetrical periventricular white matter hyperintensities

Table 1: Illustration of diverse neurological features and neuroimaging findings in Hyper-IgE syndrome

Sr. no	Age at onset of symptoms	Age at neurological symptoms	Clinical features	Lab parameters	Neuroimaging findings
1.	6 months	8.5 years	-Recurrent skin and pulmonary infections -Signs of malnutrition -Stroke and regression	IgE levels-9363 IU/ml Low lymphocyte count	Infarct in the left basal ganglia with cortical atrophy
2.	1.5 months	7.8 years	-Recurrent skin and pulmonary infections -Eczematous rash -Hyperextensible joints -Retained primary dentition -Acute encephalopathy	IgE levels- 14680 IU/ml Gene Xpert positive for MTB	Multiple tuberculomas in the cortex, brainstem and cerebellum
3.	3.2 years	3.5 years	-Ataxia -Behavioural changes -No skin or pulmonary infections	IgE levels-6067 IU/ml Eosinophilia- 53%	Symmetrical periventricular white matter hyperintensities

On further reviewing his previous investigation, the most striking finding was high total leukocyte count with eosinophilia on repeated complete blood counts. For ruling out the cause for eosinophilia, peripheral smear showed normal morphology without any blasts cells and normal retics. IgE levels were done that showed values of 6067 IU/ml. Rest of all investigations were normal, further confirming the diagnosis of Hyper IgE syndrome. This is, to the best of our knowledge, the first reported case of Hyper IgE syndrome with symmetrical white matter hyperintensities mimicking leukoencephalopathy/cerebral small vessel disease.

DISCUSSION

A gamut of neuro-radiological findings vacillating from berry aneurysms, thrombo-embolic events, chiari malformations, central retinal artery occlusion, venous angiomas and arachnoid cysts have been reported with hyper IgE syndrome. Here we present three patients with hyper IgE syndrome with diverse amalgamate of neurological features.

Vascular abnormalities manifesting as stroke (arterial or venous), foot swelling, chest pain due to myocardial ischemia has been identified as extended and rare features of hyper IgE syndrome. Malfunctioning angiogenesis, hyper eosinophilia leading to release of cytotoxic substances causing direct medial destruction and intimal dissections, and vasculitis are few possible explanations for these vascular defects.⁶ Renner et al described variable life threatening stroke presentation with ruptured cerebral aneurysm and subarachnoid hemorrhage to under-perfused large arteries and occluded small vessels of brain in children as a spectrum of hyper IgE syndrome.⁷ Our first case had left basal ganglia lenticulo-striate branch of middle cerebral artery stroke, although with a normal eosinophil count. Moreover, she had progressive symptoms apart from motor deficits with cognitive decline and loss of self-care. Martin S et al studied the relationship of focal to scattered white matter hyperintensities (WHM) with cognitive functioning and found lower scores in different domains with WMH, which could explain the regressing intellect in our index case owing to diffuse cortical atrophy, although not reported earlier.⁸

Patients with hyper IgE syndrome are prone to develop infections ranging from skin to nail infections, oral candidiasis to severe pulmonary infections, with staphylococcus aureus being the most common bug. However, fungal, viral and mycobacterium tuberculosis strains have also been less frequently isolated.¹ Neurological complications, be it infection or vascular, have more frequently been seen with autosomal recessive hyper IgE syndrome as described at Ibrahim H et al.⁴ Our second case had an overt tuberculous meningitis with

brain full of tuberculomas, with a rapid downhill course owing to the extensive involvement. There was no consanguinity that could suggest the autosomal dominant inheritance rather than recessive, although no formal genetic testing was done in this patient due to resource constraints. This highlights the close monitoring and vigilant follow up of these immune-deficient children in which small infection can spread at a whirlwind pace into an overwhelming infection leading to demise of the children.

The last case focuses on a very rare neurological presentation of a child with ataxia, tremors and behavioral issues with MRI brain consistent with bilateral symmetrical leukoencephalopathy. Purkait R et al described a case of acute disseminated encephalomyelitis with bilateral asymmetric multi focal subcortical white matter involvement⁹ and Freeman AF et al reviewed 35/50 patients ranging from 3 to 52 years of age to be having focal brain lesions, predominantly in the white matter.¹⁰ Our index case, out of all the three cases, had strikingly high eosinophilia as well, alongside symmetrical white matter lesions, which have not been previously reported to the best of our knowledge. Remarkably high eosinophilia as described earlier leads to a cascade of medial intimal injuries which possibly could give an impression like cerebral small vessel disease on MRI, though the etiology remains to be investigated.

Through this paper, we report novel imaging findings in case III and at the same time want to highlight the assemblage of clinical and neuro-radiological features associated with hyper IgE syndrome in order to expand our knowledge for better diagnosis and hence management.

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Ethical Approval: Submitted

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AUTHOR'S CONTRIBUTIONS

JRA: Conceptualization; methodology; validation; writing of original draft.

AW: Investigation; writing - review.

NG: Writing - editing

TS: Supervision; final editing and approval.