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Internal Medicine

DIAGNOSTIC DILEMMA IN TYPHOID ENCEPHALOPATHY

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ABSTRACT Using the immune system to its advantage, Salmonella Typhi initially invades the gut followed by the reticulo-endothelial system and finally the nervous system, involvement of which usually occurs around the second week of fever. In developing countries, delayed diagnosis is predominantly due to hesitation in seeking treatment. Our subject presented with fever since one week, altered mentation, headache and neck pain; she was diagnosed with enteric fever. Although her neurological abnormality could be a complication of the infection, it appeared when she became afebrile- hence we evaluated her for autoimmune conditions. Positive results hinted at autoimmune encephalitis triggered by the infection; further studies were inconclusive. Association of enteric fever with autoimmune encephalitis has not been reported. Three months later, presence of anti-nuclear antibodies (ANA) was rechecked- a negative report led to a retrospective diagnosis of transient ANA positivity in a non-autoimmune inflammatory disease, the case in point being enteric fever.

KEYWORDS : Typhoid fever, Typhoid encephalitis, Autoimmune encephalitis

INTRODUCTION

Enteric fever, also known as typhoid fever, is endemic on the Indian sub-continent. This systemic infection has a high morbidity and mortality rate. Owing to the emergence of multi-drug resistance in Salmonella Typhi, management of this disease has become more challenging. Occurrence of neuropsychiatric complications of enteric fever is approximately 45-76% in the various stages of the disease, however the chance of misdiagnosis of the primary illness can not be ruled out. (Gupta and Meena, 1992; Osuntokun et al., 1972; Wadia et al., 1985) A majority of the ambiguous instances are considered being an element of “Typhoid toxaemia”, in which the sufferers develop delirium and confusion of the preliminary stages of the sickness with high grade fever, and commonly subsides within 1-2 days of defervescence. (Nair et al., 2003) because of the vague clinical history given by the patient, rapid and affordable tests are being increasingly used, compromising on the accuracy of the diagnosis. A rapid diagnosis will help in commencing early treatment with suitable anti-microbial for rapid recovery. This will also prevent complications and mortality. (Kotpal et al., 2021)

The immune system's ability to differentiate own antigens from non-self is critical for commencing host defense against microbial antigens and safety of self-antigens from autoimmune related destruction. Autoimmune encephalitis (AE) is a group of immune-mediated non-infectious inflammatory diseases of the brain parenchyma, often affecting the cortical or deep gray matter with or without white matter, meninges or spinal cord involvement. Even though the original notion was that autoimmune affection of the brain was relatively rare, there is mounting consensus that autoimmune encephalitis is the reason behind a sub-group of altered mental status formerly considered idiopathic. The epidemiological researches that have been conducted off-late proposal that AE is likely as frequent as infectious encephalitis, with an envisioned occurrence rate of 1.3/100000. (Abbound et al., 2021) A positive ANA test is also a possibility with inflammatory diseases that are not auto-immune, including both acute and chronic infections. Use of ANA in the preliminary screening of patients with vague clinical symptoms, such as febrile spikes, arthralgias, generalized body ache, increased fatigue, rash, or deficiency of hemoglobin. (Litwin and Binder, 2016) Till date, no single diagnostic feature has been identified that may deliver this verdict in isolation, spotting a definite constellation of findings in the work's course-up of complicated and bizarre instances of new-onset altered mental status is vital to verify the diagnosis and begin treatment in a well-timed fashion. (Kelly et al., 2017)

CASE REPORT

We discuss a 48-year-old lady who was brought to Emergency Room (ER) by her spouse and daughter with a history of high grade fever and generalized weakness that started 7 days ago. Although her fever subsided after 4 days, she had complained of headache and pain over the neck for 2 days. Soon after, her family noted her develop an altered mental status which continued till her arrival at our ER. On initial assessment, her vitals were stable, but she was in an acute confusional state with irrelevant talk. There was no focal neurological deficit. No abnormality was noted on examination of the cardiovascular, respiratory and gastrointestinal system. Routine investigations into the cause of fever revealed bi-cytopenia, positivity for Typhi Dot IgM and significant Widal titer. Table 1. Magnetic Resonance Imaging of Brain with screening of the cervical spine was non-contributory. Awake Electroencephalogram (EEG) record was abnormal and suggestive of encephalopathic pattern. Image 1. A provisional diagnosis of typhoid encephalopathy was made. Despite adequate antibiotic coverage with intravenous Ceftriaxone and oral Azithromycin, there was no improvement in her mentation.

Cerebrospinal fluid analysis (CSF) analysis revealed albuminocytological dissociation. Table 2. Although her family

could not recollect any relevant positive history, a provisional diagnosis of autoimmune encephalitis was made and a trial of injection Methyl prednisolone was administered for 5 days after due consent. Meanwhile, her blood sample was sent for detection of Anti-nuclear Antibody (ANA) by HEp-2 (Human epithelial laryngeal carcinoma type 2) cell line method and showed 3+ positivity with nucleolar pattern. However ANA panel was negative. She showed dramatic improvement after receiving steroids and was soon discharged with a diagnosis of suspected autoimmune encephalitis triggered by infection with Salmonella typhi. She was followed up 15 days post-discharge and again after a month. On both these occasions, she reported an uneventful recovery and was soon back to leading her normal life. Upon detailed enquiry pertaining to any history suggestive of autoimmune conditions, her answers proved non-contributory. Before planning her long-term care, it was essential to establish a diagnosis of her auto-immune disorder by identifying specific antibodies. However, 3 months post discharge, she tested negative for the Anti-nuclear antibodies, thus giving us a retrospective diagnosis of transient elevation of ANA levels in a case of Enteric fever with encephalopathy.

Table 1. Blood investigations

Investigation & Biological range	IP Day 1	IP Day 3	IP Day 7	IP Day 10
Hemoglobin 12.0 – 15.0 g/dL	10.8	10.6	11.5	10.8
WBC count 4000-10000 /cumm	2600	7900	4500	8200
Differential count N 40-80% L20-40%	N48 L40	N60 L34	N43 L48	N81 L15
Platelet count 1.5 – 4.0 lacs/cumm	1.10	1.12	1.12	1.45
Erythrocyte Sedimentation Rate 0 – 20 mm/1st hour	111		86	
Serum Urea 13 – 43 mg/dL	19	20	14	36
Serum Creatinine 0.6 – 1.1 mg/dL	0.9	0.9	0.8	0.8
Serum Sodium 136 – 145 mEq/L	139	140	138	140
Serum Potassium 3.5 – 5.2 mEq/L	4.0	3.4	3.7	4.3
Serum Magnesium 1.7 – 2.8 mg/dL	2.2	2.2	1.9	2.4
Serum Total protein 6.4 – 8.3 g/dL	7.2	7.4	7.0	7.1
Total bilirubin upto 1.0 mg/dL	0.8	0.8	0.5	0.5
Direct bilirubin upto 0.2 mg/dL	0.1	0.1	0.1	0.1
Aspartate aminotransferase 10 – 42 U/L	46	153	65	36
Alanine transaminase 10 – 40 U/L	51	159	96	52
Alkaline phosphatase 42 – 98 U/L	103	131	114	86
Widal test STO (S. typhi somatic antigen) < 1:60 dilution STH (S. typhi flagellar antigen) < 1:60 dilution SPAH (S. paratyphi A flagellar antigen) < 1:60 dilution SPBH (S. paratyphi B flagellar antigen) < 1:60 dilution	 < 1:60 1:60 < 1:60 < 1:60			 1:120 1:240 < 1:60 < 1:60

IP Inpatient, WBC White blood cells, N Neutrophils, L Lymphocytes

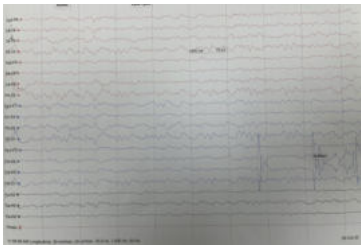

IMAGE 1. Awake EEG record showing high voltage slow wave in the range of theta waves.

Table 2. Cerebrospinal Fluid Analysis

Investigation	Test value	Biological reference
Cell type and cell count Gross Examination Appearance Coagulum Xanthochromia Microscopy Total WBC Differential count	Slightly turbid Absent Absent 3 cells/cumm 100% Lymphocytes	Clear
Glucose	58 mg/dL	Adults: 40 – 70 mg/dL
Protein	172 mg/dL	20 – 40 mg/dL
Adenosine deaminase	0.9 U/L	Normal <10 U/L; Positive >10 U/L
Acid Fast Stain	Acid Fast Bacilli not found.	
Gram Stain	No gram negative or gram positive bacteria seen in smear.	
Culture and Sensitivity	No organism grown in culture within 72 hours of incubation.	
Smear for Fungus	No fungus or fungal elements seen in smear.	
MTB DNA Detection with Rifampicin Susceptibility Gene Xpert	Mycobacterium tuberculosis DNA not detected.	
No bacteria or virus detected on Comprehensive CNS Panel.		

WBC White blood cells, MTB Mycobacterium tuberculosis, DNA Deoxyribonucleic acid, CNS Central Nervous System

DISCUSSION

Although the causative bacterium was first described more than a century ago, reliable laboratory diagnosis are inaccessible to a majority of typhoid patients. Though isolation of Salmonella typhi on blood culture remains the gold standard for diagnosis, there are many other tests including Typhi Dot, Widal and others that are widely used in developing countries. (Parry et al., 2011) The Typhi Dot usually becomes positive within 2-3 days of infection. This test is based on the detection of specific IgM and IgG antibodies. IgM signifies recent infection, whereas IgG identifies remote infection. Typhi Dot IgM has a sensitivity of 26.7% and a specificity of 61.5%. The Positive Predictive Value (PPV) was 7.4% and the Negative Predictive Value was 87.9%. A positive Typhi Dot may be due to cross reactivity between antigens of other diseases and outer membrane protein of S. typhi. (Mehmood et al., 2015) Widal titer is among the oldest and most preferred serological investigation for enteric fever, however it is usually prescribed along with other complimentary tests because of significant cross-reactivity with other Salmonella species and non- Salmonella pathogens. (Leung et al., 2012) There is a hypothesis that increased intensity of the inflammatory response is the culprit behind pathogenesis of severe typhoid, including encephalopathy. (Hornick and Griesman, 1978) Despite anti-microbial therapy being the primary modality of treatment of this disease, some observe frequently that concurrent high-dose dexamethasone therapy may have significant benefit in decreasing the case fatalities and morbidity of patients with typhoid encephalopathy. The rationale behind this school of thought is that use of steroids reduce the generation of and release of prostaglandins and free radicals by macrophages induced by Salmonella typhi endotoxin. (Leung et al., 2012)

Though the link remains controversial, there are rare case reports

on links between rheumatoid factors and typhoid fever. (Yang, 2011) Post resolution of typhoid fever, presentation of vasculitis, retinitis and macular neuro-sensory detachment, with sympathetic response to systemic steroids, has been observed. (Relhan et al., 2014) In the 20th century, Hersing and Duke-Elders documented typhoid-related uveal complications, including iritis, retinal hemorrhage, choroiditis, endophthalmitis and panophthalmitis. Association of ANA positivity with enteric fever has never has never been reported, however an association may not be completely unexpected.

Since it was first reported in 1948, the identification of ANA has been the basis for making a diagnosis of autoimmune connective tissue disease. (Satoh et al., 2009) Tests which check for presence of ANA are extensively used for diagnosis of autoimmune diseases, but ANAs are also regularly found in patients with a range of infections. Approximately 20-30% of the standard population has measurable levels of ANAs; individuals with connective tissue disorders have increased titers. (Kumar et al., 2009) Hence, the sensitivity and specificity of the method used in detecting the antibodies play a pivotal role in ascertaining the significance of the results. Positive ANA titers must be perceived in the background of existing clinical manifestations. A high ANA titer (e.g. 1:640, 1:1280 or 1:2560) implies more severe disease and further tests may be ordered to determine the type of target nuclear protein, a low ANA titer (e.g. 1:40, 1:80 or even 1:160) usually signifies no autoimmune disease, meanwhile an ANA titer in the intermediate range (e.g. 1:320) is inconclusive and should be interpreted in the clinical context. High ANA titer and positivity for multiple autoantibodies in ANAs have high specificity for SLE, while low ANA titers and presence of autoantibodies have an acute sensitivity for SLE. Hence, the odds of SLE can be judged by the ANA titer and the number of positive autoantibodies in ANAs. (Li et al., 2022)

Many contributory factors can play a role in the development of autoimmune disease. This includes stimulus from the environment, microbial infections, genetic penchant, cytokine activity etc. Diagnosing AE is challenging because of overlap in clinical presentations between the AE, other inflammatory brain diseases, infections, metabolic diseases, and psychiatric disorders. (Van Mater, 2014) A retrospective study looked into the association between infections and ANA status analysed patients that visited the Department of Infectious Diseases over 11 years and 6 months. This research inferred that several patients with the presence of these autoimmune antibodies were noted to have intracellular infections, such as mycobacterial infections, scrub typhus and syphilis. (Im et al., 2020) Viral infections have been held responsible for introducing several autoimmune diseases in people. Various mechanisms by which an infectious agent can bring upon autoimmune responses include molecular mimicry and epitope spreading. (Sherwani et al., 2018) Similarly, studies on record validate the link between false positive ANA testing and low vitamin D assay owing to immunomodulation. (Martinez et al., 2020)

Nearly 10% of Systemic lupus erythematosus (SLE) cases are induced by drugs. The detection of ANA is crucial when diagnosing SLE or drug induced lupus erythematosus (DIL). (Solomon-Tsegaye et al., 2018) While the severity of DIL is less than SLE, its diagnosis can be challenging. The presence of lupus-like symptoms after ruling out other autoimmune disorders and resolution of symptoms with the withdrawal of the offending drug suggests a diagnosis of DIL. (Kelly et al., 2018) Anti-histone antibodies are present in 3/4th of the cases of DIL, although they have limited use in differentiating DIL from SLE given a positivity in 3/4th cases of SLE as well. (Solhjoo et al., 2022) However, in our patient, absence of the usual culprit drugs in our prescription, inability to detect any specific antibody on the detail ANA panel, as well as remarkable neurological improvement without discontinuation of any drug summed up against a diagnosis of DIL.

Although no conclusive evidence has been documented to support false positive ANA levels in a background of typhoid fever, the possibility could not be ruled out completely. Once the patient completely recovered from this infection, a repeat analysis for ANA by HEp-2 method followed by complete ANA panel, solved our dilemma. This could also lead to a novel finding wherein an infection with Salmonella has triggered the autoimmune disease and manifested with neurological symptoms. Though we find up to 30 percentage positivity of ANA in the general population, its positivity in high titer and its disappearance after the patient recovered from the febrile illness is the point of interest in our case.

CONCLUSION

Autoimmune encephalitis is an essential diagnostic consideration in people presenting with acute onset mental status of uncertain etiology. Diagnosis of autoimmune conditions has always demanded a high index of suspicion. However, there also exists a risk of over-diagnosing autoimmune conditions until we rule out the false-positive cases. Physicians need to have a broad mindset towards the multitude of reasons that can give rise to certain signs and/or symptoms. An early diagnosis and proactive medical management can go a long way towards reducing case fatalities. Also, the gravity of a thorough follow-up can not be emphasized enough where the lady needed to be re-evaluated for auto-antibodies to decide on any further course of management.

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