TEACHING FILE

GRAND ROUNDS

Ira Shah

IS IT TYROSINEMIA?

Case:- A 2½ years old boy born of third degree consanguineous marriage presented with bulky frothy stools for 6 months and low hemoglobin, abdominal distension for 4 months for which he had received a blood transfusion 4 months ago. Parents also noticed bow legs for past 3 months. There was no jaundice, or polyuria. For the anemia, a bone marrow aspiration had been done that was normal. His elder brother was on treatment for leukemia. Currently, the patient was on iron, calcium and vitamin D supplements. His birth was uneventful and milestones were appropriate for age. On examination, height was 86 cm, weight was 13 kg. He had rickets with genu varus and hepatosplenomegaly. Investigations showed hemoglobin 10.9 gm/dl, white cell count 9,100 cells / cumm, platelets 91,000/cumm, bilirubin 1.4 mg/dl (direct 0.9 mg percent) SGOT 116 IU/L, SGPT 85 IU/L, total proteins 4.6 gm/dl, albumin 2.8 gm/dl, prothrombin time (PT) 21.4 sec, partial thromboplastin time (PTT) 25.6 sec, alkaline phosphatase 2120 IU/L, pH 7.436 with bicarbonate 18.0 mmol/L and alpha feto protein 8019 IU/ml. Ultrasound abdomen showed splenomegaly, nephromegaly (right kidney = 8.2 x 4.7 cm, left kidney = 8.7 x 5.8 cm) with doppler showing intrahepatic collaterals. Urine organic acids showed increased phenylalanine, lactate, glycerate, fructose, tyrosine, 4-hydroxyphenyl lactate and 4-hydroxyphenyl pyruvate suggestive of tyrosinemia though urine succinyl acetone was normal. Esophageogastroscopy showed varices in body, fundus and antrum of stomach. HIV Elisa, HBsAg and Hepatitis B were negative. He was treated with Vitamin K, folic acid, bicarbonate supplements, propanolol and diet restricted in tyrosine and phenylalanine.

Can this be tyrosinemia with normal urine succinyl acetone?

Expert's opinion:- Type I tyrosinemia is an autosomal recessive disorder affecting the tyrosine degradation pathway and leads to liver failure, Fanconi syndrome and, or rickets. (1) It is caused by a mutation in the gene encoding for the fumarylacetoacetate hydrolase (FAH) enzyme. Deficiency of this enzyme causes intracellular accumulation of fumarylacetoacetate (FAA) which is rapidly degraded to succinylacetone (SA) which is found in urine of patients with this condition. (2) Diagnosis of type 1 tyrosinemia is based on the presence of liver disease, kidney disease and, or rickets, increased tyrosine and methionine in plasma and presence of SA in urine and blood. (2) However, diagnosis can be suspected on basis of persistent asymptomatic firm hepatomegaly, mildly deranged liver functions, very high alpha-fetoprotein levels, high tyrosine levels in plasma with urinary aminoaciduria as was done in our patient. (4) Thus, we treated him as tyrosinemia. 2-(2-nitro-4-tri fluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) could not be started in this patient due to non-availability. Six months later, his bilirubin rose to 2.7 mg/dl and by the year end, he had cyanosis due to hepatopulmonary syndrome. By now, his urine SA had increased. He was advised regarding liver transplant but subsequently lost to follow up.

References

1. Scott CR. The genetic tyrosinemias. Am J Med Genet C Semin Med Genet.2006; 148: 121-126.
2. Cassiman D, Zeevaert R, Holme E, Kvittingen EA, Jacken J. A novel mutation causing mild, atypical fumarylacetoacetase deficiency (Tyrosinemia type 1); a case report. Orphanet J Rare Disease. 2009; 4: 28.

DOI No.: 10.7199/ped.oncall.2015.24

RING ENHANCING LESION IN BRAIN AND DECREASING INTERFERON GAMMA RELEASE ASSAY RESPONSE

Case: - A 14 years old boy had recurrent right focal convulsions for past 3 years. MRI brain in December 2013 showed neurocysticercosis stage II in left high parietal region for which he was treated with albendazole and steroids. In July 2014, a repeat MRI brain showed same size of granuloma. His EEG and video EEG was normal. There was history of multi-drug resistant (MDR) tuberculosis (TB) in 2 siblings of which one died in 2012 and the other was on treatment for same for the past 1½ years. In view of contact with TB, a CSF TB PCR was done which was negative. Mantoux test was negative. Quantiferon Gold test was positive (3.19). This child was not started on ATT and advised regular follow up. In December 2014, the repeat MRI showed decrease in size of granuloma and Quantiferon gold has decreased to 0.72.

How reliable is interferon gamma release assays (IGRA) for monitoring disease?

Expert's opinion:- The interferon (IFN) gamma release assays (IGRAs) are based on the fact that T-cells sensitized with tuberculous antigens will produce IFN-gamma when they are re-exposed to mycobacterial antigens. A high amount of IFN-gamma production is then presumed to correlate with TB infection. (1) The QuantiFERON®-TB Gold test (QFT-G) is a whole-blood test for use as an aid in diagnosing *M. tuberculosis* infection, including latent tuberculosis infection (LTBI) and tuberculosis (TB) disease. IGRAs are dynamic and both conversions and reversions occur when serial testing is done. This has been shown to occur among contacts as well as health care workers. There is no consensus on what the best definition for conversion is – different definitions appear to produce different rates of conversions. QFT reversions were defined as baseline IFN-gamma $\geq$ 0.35 and follow-up IFN-gamma

< 0.35 IU/ml. (2) Some reversions may reflect clearing of TB infection (spontaneous or due to treatment). Some reversions may merely be due to biological variations among IGRA positive individuals, and some reversions may be due to variability in laboratory and test procedures. Other studies suggest that reversions may occur when the mycobacterium enters a dormant state. (3,4) Thus currently IGRAs though may show reversions and conversions on longitudinal follow up of patients, interpretation needs to be with caution.

References

1. Andersen P, et al. Specific immune-based diagnosis of tuberculosis. Lancet. 2000
2. Pai M, Joshi R, Dogra S, Mendiratta DK, Narang P, et al. Serial testing of health care workers for tuberculosis using interferon-gamma assay. Am. J. Respir. Crit. Care Med. 2006` 174:349–355
3. Hill PC, Brookes RH, Fox A, Jackson-Sillah D, Jeffries DJ, et al. Longitudinal assessment of an ELISPOT test for Mycobacterium tuberculosis infection. PLoS Med. 2007` 4: e192
4. Helmy N, Abdel latif S, Kamel MM, Ashour W, El Kattan E. Role of Quantiferon TB gold assays in monitoring the efficacy of antituberculosis therapy. Egyptian Journal of Chest Diseases and Tuberculosis. 2012; 61: 329–336

DOI No : 10.7199/ped.oncall.2015.22

PRE-EXTENSIVE DRUG RESISTANT (XDR) TUBERCULOSIS

Case: - A 14 years old girl presented with low grade fever for 8 months along with loss of weight and appetite. She had received 3 drug antituberculous therapy (ATT) 2 years ago for 6 months in view of positive mantoux test. On examination, her weight was 28.2 kg, height was 148 cms. Systemic examination was normal. Chest X-Ray was normal. Ultrasound of abdomen showed multiple mesenteric lymph nodes with largest being 2 x 1.5 cm. CT abdomen showed multiple necrotic lymphnodes. CT guided biopsy of lymph node showed granulomas and tuberculosis (TB) culture did not grow *mycobacterium tuberculosis* (MTB). She was started on 4 drug antituberculous therapy with 2 drugs as continuation phase. At end of 4 months of therapy, her weight was 32 kg but ultrasound showed increase in size of nodes to 3.6 cms. At end of 7 months of therapy, the nodes were the same but weight had increased to 37 kg. At end of 1 year of therapy, nodes had regressed in size (largest being 2.7 cm) and weight was 40.6 kg. ATT was stopped. After 3 months of stopping ATT, she presented with amenorrhea for 1½ months and fever for 15 days. She had achieved her menarche one year ago and menses were regular every 28 days. A repeat ultrasound abdomen was done that showed hypoechoic mass in right iliac fossa 6.8 cm x 2.8 x 2.0 cm adherent to the right ovary. A CT guided aspiration of the pus was done. She was started on IV ceftriaxone, metronidazole for the right tubo-ovarian mass along with medroxy progesterone for 5 days following which she had withdrawl bleeding. Her pus culture grew extended spectrum beta lactamase (ESBL) producing E.coli sensitive to carbapenems, amikacin, and colistin. She was shifted to IV Meropenem and fever responded to the same. TB culture after 6 weeks grew MTB resistant to isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S) and moxifloxacin (Mfx) but sensitive to aminoglycosides, PAS, ethionamide and clofazimine.

What should be her ATT schedule now?

Expert's Opinion :- This child has pre-extensive drug resistant (XDR) TB with resistance to both HR and even quinolones. Multidrug-resistant (MDR) TB implies resistant to both isoniazid and rifampicin whereas XDR TB implies MDR TB with additional resistance to at least a flouroquinolones and one of the injectables i.e. kanamycin, amikacin or capreomycin. (1) Since she has resistance to quinolones but not to aminoglycosides, she has pre- XDR TB. She would need to be started on second line ATT. Drugs are chosen with a stepwise selection process through five groups. Among the first group (the oral first-line drugs) high-dose isoniazid, pyrazinamide and ethambutol are thought of as an adjunct for the treatment of MDR and XDR tuberculosis. The second group is the injectable drugs (capreomycin, kanamycin, amikacin). The third group include the flouroquinolones. The fourth group are called the second-line drugs (thionamide, cycloserine and aminosalicylic acid). The fifth group includes drugs that have sparse clinical data (clofazimine, amoxicillin with clavulanate, linezolid, carbapenems, thioacetazone and clarithromycin). (2) In this child since all the first line drugs were resistant, the child was treated with amikacin, cycloserine, PAS, clofazamine and linezolid. She received injectable for 6 months and remaining drugs for 20 months. She responded to her therapy.

References:

1. World Health Organization (WHO) Global Tuberculosis Control Report 2011. Available at website: ww.who.int, tb, publications, global_report, 2011, gtbr11_full.pdf. Accessed on 8th March 2012
2. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010` 10: 621-629.

DOI No. : 10.7199/ped.oncall.2015.23

From: Medical Sciences Department, Pediatric Oncall, Mumbai.

Address for Correspondence Dr Ira Shah, 1/B Saguna, 271, B St Francis Road, Vile Parle (W), Mumbai 400056.