Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi:

Refractory hypocalcemia precipitated by dual infection with typhoid fever and hepatitis A in a patient with congenital hypoparathyroidism

Suman S Karanth*, Ram Bhat, Anurag Gupta

Kasturba Medical College, Manipal, Manipal University, Karnataka, India

ARTICLE INFO

Article history:
Received 10 March 2012
Received in revised form 15 May 2012
Accepted 15 July 2012
Available online 20 August 2012

Keywords:
Refractory hypocalcemia
Typhoid fever
Hepatitis A

ABSTRACT

We present this rare occurrence of a 17 yr old boy, a known case of congenital hypoparathyroidism, who presented with fever and jaundice for 8 days and 2 episodes of generalised tonic-clonic seizures. Premorbidly patient was on regular oral calcium supplementations with normal serum calcium levels. Investigations revealed severe hypocalcaemia (3.2 mg/dL), low 25 hydroxyvitamin D levels and hypomagnesaemia. The marked elevation of serum bilirubin was accompanied by derangement of liver enzymes. Microbiological investigations were confirmatory for both hepatitis A and typhoid fever. In spite of the aggressive management with intravenous calcium gluconate infusion, refractory hypocalcaemia persisted with recovery only after gradual decline in the bilirubin levels. We inferred that the cholestatic process produced by both acute viral hepatitis A and typhoid fever precipitated this state of refractory hypocalcaemia in the previously well preserved patient.

1. Introduction

Hepatitis A can present infrequently as cholestatic hepatitis[1]. Typhoid fever can also present with acute hepatitis along with cholestatic jaundice[2]. Normally this cholestatic phenomenon is clinically benign. However we would like to report this perplexing case where both these infections combined to produce refractory hypocalcemia in a patient with previously stable congenital hypoparathyroidism.

2. Case report

A 17 yr old boy, a known case of congenital hypoparathyroidism on regular treatment of oral calcium supplementations, presented to us with fever and jaundice for 8 days associated with 2 episodes of generalised tonic-clonic seizures on day 3 of fever. He was diagnosed to have congenital hypoparathyroidism at 2 ½ years of age when he presented with febrile seizures and hypocalcemia. There were no signs of rickets, steatorrhea or alkalosis at the time. Skull and wrist rhoentograms were normal. But computed tomography of the brain showed extensive bilateral deep basal ganglion calcification. Patient was receiving regular oral calcium supplementation (1 g *tid*) with calcitriol (0.25 microgm *bd*) ever since and serial serum calcium levels were normal. When the patient presented to us 8 days later, he continued to have high grade fever with chills and rigors and without further episodes of seizures. Clinical examination revealed the stigmata of congenital hypoparathyroidism with dystrophic nails and teeth. There was, however, no evidence of growth retardation or developmental delay. Chvostek and trousseau sign were positive. He had no history of any preexisting liver disease and denied alcohol abuse, the use of drugs known to be hepatotoxic, blood transfusion , drug addiction, unsafe heterosexual and/or homosexual exposure or surgery in the previous 6 months.

Vitals were stable except for febrile state. Icterus was present. Liver was enlarged 3 cm below the right costal margin and a soft spleen was palpable 2 cm below the left costal margin. Investigations revealed severe hypocalcemia (3.2 mg/dL-corrected for hypoalbuminemia),raised phosphorus levels (5.4 mg/dL), and hypomagnesia levels (1.2 mg/dL). Total bilirubin (TB) was grossly deranged (11.2 mg/dL) with a predominant direct hyperbilirubinemia (DB) (9.2 mg/dL). Liver enzymes were deranged [serum glutamic-oxaloacetic transaminase: 289 mg/dL, serum glutamic-pyruvic transaminase: 699 mg/dL, alkaline phosphatase (ALP): 400 mg/dL] with a prolonged prothrombin time, high gamma-glutamyltransferase and low albumin.

*Corresponding author: Dr. Suman S Karanth, #17 OPD Block, Department of Medicine, Kasturba Medical college, Manipal, Manipal University, Karnataka, India.
Tel: +91-776-023-1806
E-mail: drsumansk@gmail.com

25 hydroxyvitamin D levels were low. Microbiological investigations revealed a positive anti hepatitis A virus (HAV) of IgM class but negative to antibodies for hepatitis B surface antigen and hepatitis C virus. He also tested negative for antibodies to HIV. Widal test was positive with titres of O: 1: 320 , H : 640. Serial blood cultures grew *Salmonella typhi*. Patient was started on parenteral ceftriaxone. In view of severe hypocalcemia, parenteral calcium gluconate was administered immediately along with oral correction with calcium supplements, calcitriol and magnesium. By day 2 of admission the hypomagnesemia was corrected with no improvement in the serum calcium levels. Inspite of aggressive management, serial calcium levels remained low with persistence of carpopedal spams. On Day 4, TB peaked to 20 mg/dL with a DB of 14 mg/dL and calcium levels being the lowest (corrected value 3.0 mg/dL). By day 7, there was a gradual decline in bilirubin and ALP levels which was accompanied by a steady rise in the calcium levels. Day 8 onwards the patient was gradually weaned off the parenteral calcium therapy gradually. By day 11 the parenteral therapy was stopped and the patient was continued on both oral calcium and calcitriol at a high dose which was also gradually tapered. Antibiotic therapy was continued for a 14 day period. Clinically, the patient recovered completely with normalization of the liver enzymes and prothrombin by day 15 and he was discharged with the premorbid dose of oral calcium supplementations.

3. Discussion

Congenital hypoparathyroidism is either autoimmune or due to genetic mutations in either the parathyroid hormone (PTH) genes, calcium sensing receptors , transcription factors or mitochondrial DNA[3]. Hypoparathyroidism is diagnosed when the intact PTH level is normal or inappropriately low after ruling out hypomagnesemia. Serum phosphorus levels are usually high[3]. The resultant hypocalcemia can present as asymptomatic in mild cases to acute life-threatening crisis in severe cases[4]. Abnormalities in levels of vitamin D also contribute to hypocalcemia. The role of 1, 25-dihydroxyvitamin D is to enhance the intestinal absorption of both calcium and phosphorus[5,6]. Inadequate vitamin D levels can lead to 50% reduction in intestinal calcium absorption. This leads to only 10%-15% of dietary calcium being absorbed[5]. As our patient was a previously worked up case of congenital hypoparathyroidism, we did not investigate it further. In view of persistent hypocalcemia despite aggressive therapy, we suspected a coexisting vitamin D deficiency. At this admission, we found a previously normal 25 hydroxy vitamin D level to be low.

In adults, hepatitis A is often symptomatic with rare occurrence of fulminant form[7]. The disease severity varies with pre-disposing host factors, such as increased age or existence of an underlying chronic liver disease[1]. Atypical clinical presentations like prolonged hepatitis, cholestatic hepatitis and relapsing hepatitis though rare are known to occur with hepatitis A infection[8].Typhoid fever, similar to hepatitis A causes mild hepatitis and persistent fever[9,10]. There are a few case reports of severe cholestasis following both acute hepatitis A infection[1] and typhoid fever[2,11,12]. Studies on the impact of viral hepatitis on vitamin D levels though limited, have shown to produce a steady decline in vitamin D levels[13].

We ventured into the hypothesis that the cholestatic process caused by this dual infection resulted in low 25 hydroxy vitamin D levels and a subsequent decreased absorption of calcium, precipating this state of refractory hypocalcemia. This was justified by observing lowest serum calcium levels corresponding to the peak bilirubin levels. A gradual improvement in the serum calcium levels which paralled the steady fall in bilirubin levels supports the hypothesis. At discharge, we were able to send the patient on his premorbid dose of oral calcium. At subsequent follow up, patient was better. To our best knowledge, this is the first case report of severe refractory hypocalcemia due to absorptive defects caused by simultaneous infection with both enteric fever and hepatitis A. Though such a phenomenon of absorptive defects is known, its clinical implications are underestimated. This may land a clinician in a therapeutic predicament. Clinicians need to be aware of this for a prompt diagnosis and appropriate therapy.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Coppola N, Genovese D, Pisaturo M, Taffon S, Argentini C, Pasquale G, et al. Acute hepatitis with severe cholestasis and prolonged clinical course due to hepatitis A Virus Ia and Ib Coinfection. *Clin Infect Dis* 2007; **44**(9): 73-77.

[2] Albayrak A, Gunbey SS, Aktas F. Cholestatic hepatitis due to *Salmonella typhi*. *Clin Pract* 2011; **1**(1).

[3] Shoback D. Hypoparathyroidism. *N Engl J Med* 2008; **359**: 391-403.

[4] Cooper MS, Gittoes NJ. Diagnosis and management of hypocalcaemia. *BMJ* 2008; **336**(7656): 1298-1302.

[5] Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357**(3): 266-281.

[6] Walker Harris V, Jan De Beur S. Postoperative hypoparathyroidism: medical and surgical therapeutic options. *Thyroid* 2009; **19**(9): 967-973.

[7]Abdel-Hady El-Gilany, Hammad S, Refaat K, Reda Al-Enazi Seroprevalence of hepatitis A antibodies among children in a Saudi community. *Asian Pac J Biomed* 2010; **3**(4): 278-282.

[8] Sagnelli E, Coppola N, Marrocco C, Onofrio M, Scarano F, Marotta A, et al. HAV replication in acute hepatitis with typical and atypical clinical course. *J Med Virol* 2003; **71**(1): 1-6.

[9] Mirsadraee M, Shirdel A, Roknee F. Typhoid myopathy or typhoid hepatitis: a matter of debate. *Indian J Med Microbiol* 2007; **25**(4): 351-353.

[10] Mishra D, Chaturvedi D, Mantan M. Typhoid fever and viral hepatitis. *Indian J Pediatr* 2008; **75**(5): 509-510.

[11]Yap I, Wee A. Uncommon presentation of typhoid fever: a case report. *Ann Acad Med Singapore* 1993; **22**(6): 943-944.

[12]Ahmed A, Ahmed B. Jaundice in typhoid patients: Differentiation from other common causes of fever and jaundice in the tropics. *Ann Afr Med* 2010; **9**: 135-140.

[13]Daniel D Bikle. Vitamin D insufficiency/deficiency in gastrointestinal disorders. *J Bone Mineral Res* 2007; **22**(S2): 50-54.