Biotinidase deficiency—masquerade of primary immunodeficiency disease in neonate

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SUMMARY

Biotinidase deficiency, a rare metabolic disorder characterised by abnormal biotin metabolism, affects the biotin-dependent carboxylase functions. Primarily characterised by neurological and skin disorder, it may present with myriad features. Early recognition is important for preventing long-term morbidities. Here, we describe a case of a neonate presenting with seizures and a clinical picture suggestive of immunodeficiency. Multiple superficial abscesses along with septic arthritis of the left knee and left hip led to suspicion of primary immunodeficiency disorder. On evaluation, there was severe biotinidase deficiency. The neonate was supplemented with biotin, after which there were no further episodes of severe infection requiring hospitalisation, seizures or skin manifestation. This case report highlights the wide spectrum of clinical picture these disorders may present with and the low threshold for their evaluation and treatment.

BACKGROUND

Biotinidase deficiency (BTD) is an autosomal recessive neurocutaneous disorder and may present from the neonatal period to adulthood.[1 2] Incidence of BTD varies from 1:40 000 to 1:60 000 live births.[1] Biotinidase is an enzyme that frees up the vitamin biotin from biocytin and dietary protein-bound sources (figure 1). Biotin acts as a coenzyme for multiple carboxylase enzymes; thus, BTD may present with multisystem involvement.[3] The most common presentation includes neurological features like hypotonia, seizures, developmental delay, hearing loss, optic atrophy, ataxia and dermatological manifestations like alopecia and skin rashes[2 4] Many atypical features like respiratory distress, tachypnoea, paroxysmal attacks of head dropping and high anion gap metabolic acidosis may make its diagnosis challenging.[5 6] Neonatal presentation is rare but may present with dermatitis, alopecia, encephalopathy and seizures[4 7] Here, we present a case of BTD, where the neonate presented with multiple superficial abscesses, left knee and hip septic arthritis along with seizures.

CASE PRESENTATION

A term 2.4 kg male baby, with uneventful antenatal and perinatal history, born by normal vaginal delivery from a non-consanguineous marriage, presented to the emergency department at day of life (DOL) 16 with a history of abnormal movements of the right upper limb with frothing and uprolling of eyes for 15–20 s. There was no prior history of seizure in the baby. There was also associated swelling, redness and pain in the left knee and hip for the past 4–5 days, with decreased movements of the left lower limb. The neonate had multiple superficial abscesses of 2–3 cm on the right and left forearm and wrist area. At the presentation, the baby had respiratory distress for which the baby was intubated and put on mechanical ventilation. There were no skin rashes or any other dermatological manifestations. Blood sugar and electrolytes were normal. Antibiotics (meropenem and vancomycin) were started with a provisional diagnosis of sepsis, meningitis and pneumonia with septic arthritis. Septic screen was done which came positive with increased C reactive proteins and thrombocytopenia (table 1). Blood culture grew *Streptococcus pyogenes*. Lumbar puncture came normal ruling out meningitis. Cranial ultrasound (USG) was normal. Ophthalmological examination conducted was normal. Knee and hip USG was suggestive of septic arthritis (collection with internal echoes present). Left knee aspiration was done at DOL 23 which came out sterile. Gradually superficial abscess improved with conservative management. The baby improved and was extubated, and room air trial was given at DOL 26. Hip joint collection improved, but knee septic arthritis persisted, for which the patient underwent left knee arthrotomy at DOL 34, after which there was gradual improvement in the condition. One packed red blood cell transfusion was required at DOL 34 in view of severe anaemia. Intravenous antibiotics were continued for 5 weeks, which were followed by 6 weeks of oral cefixime and linezolid.

In view of multiple foci of infection, immunodeficiency was suspected. There was no significant family history suggestive of primary immunodeficiency disorder. Patient serology for HIV was non-reactive. The neonate's leucocyte count, lymphocyte count, lymphocyte subset count and immunoglobin profile were within the normal range (table 1). Arterial blood gas after stabilisation showed normal pH and bicarbonate levels (pH - 7.36; standard bicarbonate - 22 mmol/L). Clinical exome sent for primary immunodeficiency disorders was suggestive of BTD (heterozygous for BTD NM_001370658.1 gene, variant c.124G>A p.Val42Met). This was followed by serum biotinidase activity which was less than 10% of normal enzyme level. The neonate was started on tablet biotin 10 mg/day. For supportive therapy in the form of hydration, bicarbonate therapy was considered—but was not required as the baby improved with improvement in sepsis. Genetic counselling of the parents was done regarding the condition. Possibility of recurrence in the family was explained. Workup of the

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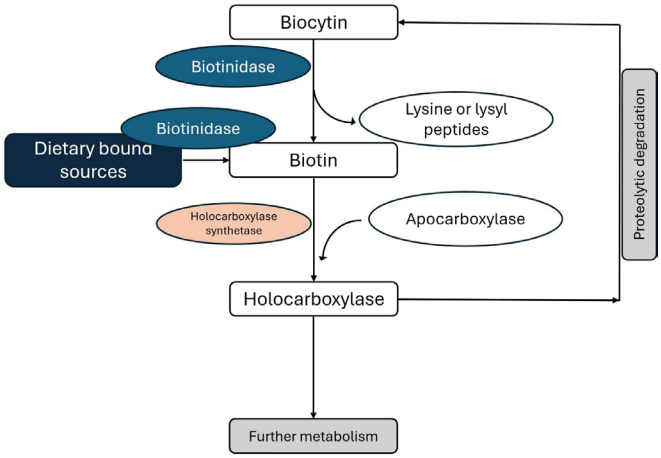

Figure 1 Biotin cycle.

parents was also advised, which they refused. With improvement in condition, the baby was discharged at DOL 52 and was followed up in outpatient department.

INVESTIGATIONS

DIFFERENTIAL DIAGNOSIS

Primary immunodeficiency disorders like severe combined immunodeficiency, combined immunodeficiency disorders like hyper IgM syndrome, Wiskott-Aldrich syndrome and hyper-IgE syndrome were considered differentials. These were ruled out in view of normal blood cell counts, immunoglobin profile and genetic workup. Inborn error of metabolism like organic acidemias and other carbohydrate and lipid metabolism defects, which may present with immunodeficiencies, was also considered. Normal basic metabolic profile (normal lactate levels, negative urinary ketones, euglycemia and pH within normal range) post-stabilisation of the baby further ruled out these conditions. Ammonia level could not be sent in view of logistic issues and then clinical improvement of the baby. It remains an important investigation and should be planned in such cases.

OUTCOME AND FOLLOW-UP

The infant was followed up until 6 months of age. There were no repeated episodes of seizures, serious infections requiring hospitalisation or any skin or hair lesions. On follow-up, the baby is thriving well and has attained all the developmental milestones as per age. There is no restriction of movement or pain in the left lower limb. Ophthalmological evaluation for eye involvement and brainstem evoked response audiometry were within normal range. The parents have been advised about the need to continue lifelong biotin therapy, for regular follow-up to monitor for development and vision and hearing assessment, and to look for any clinical signs due to biotin deficiency.

DISCUSSION

BTD is screened at birth in many countries. Timely detection and supplementation with oral biotin may prevent most of the

Table 1 Relevant investigations during hospital stay

	DOL 16	DOL 21	DOL 23	DOL 26	DOL 32	DOL 34	DOL 35	DOL 41
Hb (g/L)	116.8		110.6	111.7	87.3	79.1	101.3	
TLC (/cumm)	21 900		16 500	12 640	9160	9000	17 810	
ANC (/cumm)	15 480		11 550	7860	2970	3870	9360	
Absolute lymphocyte count (/cumm)	4920		3480	2860	3770	3780	5710	
Platelet (10^9/L)	40		124	126	200	229	173	
CRP (mg/L)	61		78	73	104		54	51
Na (mmol/L)	136							
K (mmol/L)	4.5							
Ca (mg/dL)	7.09			7.85	8.17			
Creatinine (mg/dL)	0.35							
Urea (mg/dL)	21							
SGPT (U/L)	21							
SGOT (U/L)	33							
ALP (IU/L)	310							
Serum proteins (g/dL)	3.71			4.02				
Serum albumin (g/dL)	1.99			2.12				
Immunoglobin levels (mg/dL)								
IgM		72.38						
IgG		642.49						
IgA		22.4						
Lymphocyte subset count (/cumm)								
Absolute lymphocyte count		2871						
CD3+ T cell		2153						
CD4+ Th cell		1378						
CD8+ Tc cell		446						

ALP, alkaline phosphatase; ANC, absolute neutrophil count; Ca, calcium; CRP, C reactive protein; DOL, day of life; Hb, haemoglobin; Ig, Immunoglobin; K, potassium; Na, sodium; SGOT, serum glutamate-oxaloacetate transaminase; SGPT, serum glutamate-pyruvate transaminase; TLC, total leucocyte count.

symptoms before the disease manifests. In symptomatic individuals, biotin may improve most of the problems; however, auditory and visual symptoms may not reverse.[8] If not treated in time, affected individuals may have irreversible neurological damage or may decompensate and go into coma and die.[9] Here lies the importance of early suspicion and timely diagnosis of BTD. BTD is detected by low enzyme activity and mutation analysis. BTD may be partial, that is, enzyme activity between 10% and 30% or maybe profound with enzyme activity less than 10%.[10] Patients with partial deficiency have milder symptoms and may present later on, whereas profound BTD generally presents with seizures and requires more aggressive follow-up and treatment.[10 11]

BTD leads to deficient-free biotin available for the four carboxylase enzymes—pyruvate carboxylase, propionyl-coenzyme A carboxylase, methylcrotonyl-coenzyme A carboxylase and acetyl-coenzyme A carboxylase. These enzymes play a central role in a multitude of cellular metabolism. This explains the multisystem nature of the disease. It may also explain the immunodeficiency and recurrent infections present in patients suffering from BTD. Cowan *et al* reported three affected infants aged 2–3 months of life, presenting with systemic infections, whose immunodeficiency workup showed selective IgA deficiency in one and failure to develop specific antibodies in response to immunisation and abnormal cell-mediated responses to antigen in the other two.[12] Fischer *et al* reported a 12-month-old infant with infections, who had carboxylase deficiency and linked it to the deficient prostaglandin E2 synthesis as the abnormal immune response was corrected in vitro by adding prostaglandin E to the medium.[13] In another case report, a 3-year-old girl presented with recurrent infections, candidiasis and skin rashes. She was diagnosed with BTD.[14] Her immunoglobulin levels and lymphocyte subset analysis were within the normal range. Her unresponsiveness to candidin skin test suggested an impaired T lymphocyte function to *Candida* antigen. Our patient had profound BTD and presented with septic arthritis with multiple superficial abscesses. Immunoglobin profile and lymphocyte subset counts were within normal range. To the best of our knowledge, this is the first case report where a neonate with BTD presented with features mimicking a primary immunodeficiency disorder. This case highlights the importance of suspecting BTD in neonates with severe or recurrent infections suggesting immunodeficiency, for early diagnosis and treatment to prevent long-term morbidities.

Learning points

- Biotinidase deficiency (BTD) may present with myriad clinical features including skin manifestations, neurological problems, respiratory distress and metabolic disorders among others and should be suspected in any patient with multisystem involvement.
- It is important to consider BTD as a potential underlying cause of immunodeficiency-like symptoms in neonates.
- Early diagnosis and intervention with biotin supplementation may improve the outcomes and prevent further complications due to BTD.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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