Iatrogenic Severe Protein Deficiency in a Child

Sir,

A significant proportion of inborn error of metabolism (IEM) present during neonatal period with non-specific symptoms like lethargy, poor feeding, vomiting and tachypnea. This causes delay in diagnosis and appropriate management of IEM, presenting in neonates and often leads to inappropriate treatment like protein restriction. Therefore, appropriate laboratory testing for metabolic disorders should be performed in any infant who exhibits these symptoms before starting low protein diet.

A baby girl was born at term to first-cousins parents following an uncomplicated pregnancy; with birth weight of 4 kg, length of 50 cms and head circumference of 34.5 cms. The infant was bottle fed but was noted to be dull and had an episode of vomiting on day 1 of life. Her oral feed were stopped and sepsis was considered.

On day 4 of life, treating physician considered IEM and ordered plasma ammonia as the only screening test for IEM, which was sent from the primary hospital to our laboratory, ammonia came as 262 mmol/L. It took more than 7 hours to get ammonia results. This was considered high and the infant was declared to have an IEM and was started on an ammonia scavenging medicine; oral sodium-benzoate (Na-benzoate) and a protein-free powder. After 10 days, she was discharged from the primary hospital without any confirmatory metabolic tests.

The baby was followed-up by primary pediatrician for one month on zero protein and oral Na-benzoate. At 30 days of age, baby started showing severe protein deficiency signs including exfoliative erythema around genitalia and profuse diarrhea.

She was brought to our hospital on 40th day of age and was noted to have pedal edema, angular cheilitis, easily pluckable hair and extensive exfoliative erythema involving legs, back and arms. She weighed only 3.2 kg.

The infant was investigated according to protocol outline in Table I. All first line investigation including plasma ammonia were normal. Serum albumin was only 1.7 gm/dl reflecting severe protein deficiency. After collecting samples for second line investigation, she was started on 0.5 gm/kg/day of natural protein. Calories were topped up with a protein free formula. Gradually her feeding was increased and protein intake was built-up reaching 1 gm/kg/day over next 3 days. Her second line investigations were sent to Institute of Medical Research, Kuala Lumpur for diagnostic purpose, which excluded an IEM needing protein restriction or Na-benzoate, after which, her protein intake was liberalized and oral Na-benzoate was stopped. In 3 weeks, skin healed and she was discharged at 3.6 kg.

When there is suspicion of IEM then specific diagnostic tests and management should be undertaken in consultation with Metabolic Specialist. Interpretation of plasma ammonia concentration can raise problems. A difficult venepuncture, a struggling child or delay in processing all leads to spurious high level. Muscle exertion may increase venous ammonia level, therefore; patient's arm should be as relaxed as possible. Blood should be collected in a chilled heparinized vacuum tube, which should be immediately placed on ice. Plasma should be separated from blood within 15 minutes of sample collection. After blood collection, it is essential to maintain temperature at 4°C because ammonia level of standing blood and plasma rises spontaneously. Most of this increase has been imputed to release of ammonia from red blood cells and deamination of amino-acids, mainly glutamine. Plasma ammonia levels of a whole blood maintained at 4°C are stable for < 1 hour. When plasma is readily separated from blood then, plasma

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Table I: Suggested laboratory tests for infants in whom inborn error of metabolism is considered.

**First-line investigations:**
1. Urea and serum electrolytes.
2. Anion gap.
5. Plasma lactate.
6. Plasma ammonia.
7. Urine reducing sugars.
8. Urinary ketones
9. Complete blood count with differentials.

**Second-line investigations:**
1. Dried Blood spots for amino acids and acylcarnitines *
2. Urine organic acids.
4. Plasma carnitine.

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* Dried Blood spots are used for newborn screening of IEM in many countries. Since newborn screening for IEM is not done in Pakistan, therefore; it is included in second-line investigations instead of first-line investigation.

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Figure 1: Clinical photograph showing angular cheilitis, easily pluckable hair and extensive exfoliative erythema.
ammonia levels are stable at 4°C for 4 hours and for 24 hours if plasma is frozen at -20°C. For healthy neonates plasma ammonia is < 65 mmol/L, any sick newborn may have values upto 180 mmol/L. Plasma ammonia > 200 mmol/L suggest a metabolic disorder, and should be immediately investigated further.

Plasma ammonia is not routinely checked in most hospitals in Pakistan. Often blood is collected and sent to distant laboratories without maintaining appropriate temperature and following proper collection method. Physicians often do not assess the method of sampling and do not debate high ammonia values secondary to delayed processing. Similarly, it is inappropriate to diagnose a patient as IEM without doing second line laboratory testing. The child described here was not only treated with Na-benzoate unnecessarily but was also subjected to a zero protein diet for so long that she developed severe protein deficiency.

It is important to realize that protein cannot be withheld indefinitely. Till a final diagnosis is pending, some protein should be introduced after a maximum of 2-3 days of protein restriction. Initially 0.5 gms/kg/day is allowed and is gradually increased to 1.0 gm/kg/day and held at that level until diagnosis is finalized and definitive long-term treatment plans are made. After proper diagnostic tests, she was found to have no IEM, therefore; required neither protein restriction nor Na-benzoate. She recovered from profuse diarrhea and her skin healed to normal when her protein intake was liberalized.

REFERENCES


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