

Inborn Errors of Metabolism Presenting as Neonatal Encephalopathy: Practical Tips for Clinicians

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Abstract

Inborn errors of metabolism constitute an important cause of neurological disease in the neonatal period and can present clinically as encephalopathy. Although it is relatively rare, it is important to have a high index of suspicion. Appropriate investigations and a step-wise approach to diagnosis allow for early institution of treatment and can prevent significant morbidity and mortality. The aim of this article is to give a brief outline of the various inborn errors of metabolism to consider in neonatal encephalopathy and to provide a framework for investigation and diagnosis.

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Neonatal encephalopathy is a clinically defined syndrome of disturbed neurological function in the infant during the first week after birth, manifested by difficulty initiating or maintaining respiration, depression of tone and reflexes, altered level of consciousness and often seizures. Encephalopathy can be subtle in the neonatal period and can be missed unless signs are specifically looked out for.¹ This can range from poor suck and jitteriness to seizures and apnoea. Seizures in a neonate may not be the typical tonic clonic seizures, but a series of brief jerks or spasms of muscles of the face, limb, and tongue. They can also present with brief fixation or eyelid flutter, sucking movements or apnoea.

There are many causes of neonatal encephalopathy and inborn errors of metabolism are rare causes. However, it is important to have a high index of suspicion as early diagnosis and intervention can significantly alter the prognosis. Acute encephalopathy due to metabolic disorders usually result from accumulation of a toxic substance e.g. ammonia or deficiency of an essential product e.g. ATP.² Most of these metabolites are able to cross the placenta and therefore the baby is usually well at birth. A typical history would be a baby who was well initially, but only to present with poor feeding, lethargy or seizures after a few days.

Inborn errors of metabolism presenting with encephalopathy can broadly be divided into 2 main groups, one with significant biochemical abnormalities and another

group with none. It is essential to do baseline investigations to further classify these patients. Baseline investigations would include a plasma electrolytes, ammonium, amino acids, lactate, acid-base status and glucose level. Urine sample for ketones and organic acids are also useful (Table 1).

Encephalopathy with Significant Biochemical Abnormalities

(i) Hyperammonemia

When there is significant hyperammonemia, the main metabolic disorders to exclude are urea cycle defects and organic acidurias.³ As these disorders mainly affect the protein metabolism, they often present after the baby has established full feeds. The presence of significant metabolic acidosis in organic acidurias distinguishes the 2 groups of disorders as acidosis is usually severe in organic acidurias. Other rare causes of hyperammonemia to consider are fatty acid oxidation disorders and transient hyperammonemia of the newborn.

Ammonium is neurotoxic. Neurological damage and the eventual prognosis is dependent on the duration and severity of hyperammonemia. Therefore, it is essential to institute urgent treatment. All protein intake should be stopped and adequate caloric intake ensured. Treatment includes intravenous sodium benzoate or sodium phenylbutyrate. Severe or refractory cases may require hemodialysis or

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Table 1. Investigations for Neonatal Encephalopathy

Baseline investigations
Electrolytes, calculate anion gap
pH and blood gases
Glucose
Plasma ammonium
Plasma lactate
Urine ketones
Plasma amino acids
Urine organic acids
Second-line investigations
Plasma carnitine and acylcarnitine profile
Urine amino acids
Urine reducing sugars
CSF amino acids
CSF glucose
CSF neurotransmitters

hemofiltration. Other medications may be required depending on the metabolic disorder suspected.

(ii) Metabolic Acidosis

A common laboratory feature of many inborn errors of metabolism during an acute illness is metabolic acidosis with an increased anion gap. A few of these conditions can present acutely in the neonatal period with mainly neurological symptoms. These can be divided into the main anions that cause the acidosis.

Lactic acidosis

Lactic acidosis can be a common acute feature in critically ill neonates, often as a result of poor circulatory perfusion or seizure activity. However, persistent lactic acidosis or increased lactate in the cerebrospinal fluid is suggestive of metabolic disease. In a neonate with encephalopathy and persistent lactic acidosis, one needs to exclude mitochondrial defects or pyruvate metabolism defects.⁴

Organic acidurias

Organic acidurias such as methylmalonic acidemia (MMA) and propionic acidemia (PA) are disorders of branched-chain amino acid metabolism.⁵ Metabolic decompensation often occurs in the first week of life after establishing feeds and is heralded by signs of encephalopathy accompanied by marked metabolic acidosis. This is also usually accompanied by hyperammonemia as a result of a secondary inhibition of the urea cycle. Urine organic acid analysis would show excretion of the abnormal organic acid and is often diagnostic.

Acute management of organic acidurias includes removal of offending substrate and ensuring adequate caloric intake. Administration of carnitine facilitates the excretion of the organic acids. In addition, cofactors such as vitamin B12 or biotin are often given during the acute illness as the patient might have a vitamin B12 responsive MMA or some patients with multiple carboxylase deficiency are responsive to biotin.³ Treatment for secondary hyperammonemia may be necessary.

(iii) Hypoglycaemia

Hypoglycaemia can be a presenting feature in many metabolic diseases. The timing of hypoglycaemia in relation to feeds can be very useful in directing the next line of investigations.⁶ If hypoglycaemia occurs shortly after a feed, one should always suspect hyperinsulinism. Disorders of gluconeogenesis can present after fasting of a few hours e.g. Glycogen storage disease type I. Hypoglycaemia can also be a presenting symptom of galactosaemia.

Fatty acid oxidation defects are also an important group of conditions to consider in hypoglycaemia.⁷ These neonates have an impaired capacity to use stored fat as a source of energy during periods of fasting. Other clinical features include hepatomegaly, myopathy and Reye syndrome. Urine organic acid analysis, measurement of plasma carnitine and acylcarnitine profile are the main line of investigations. Confirmatory studies can be performed on skin fibroblast or mutation analysis.

Encephalopathy with no obvious biochemical abnormalities

However, there are several other causes of neonatal encephalopathy that may not have any biochemical clues. Non-ketotic hyperglycinemia (NKH) typically presents in the first few hours or days of life with refractory seizures and progressive obtundation.⁸ The presence of hiccups may be a clue. Diagnosis is based on an increased CSF: plasma glycine ratio.⁹ Treatment in classical NKH is often disappointing and mortality is high. Survivors will have profound neurological sequelae.

Maple syrup urine disease (MSUD) can also present with deepening encephalopathy in the first week of life. There is accumulation of branched chain amino acids (BCAA), due to decreased activity of branched-chain ketoacid dehydrogenase complex. Leucine in particular is neurotoxic. These patients may not have any significant biochemical abnormality apart from ketosis and occasional hypoglycaemia. Plasma amino acid analysis reveals increased leucine and allo-isoleucine levels. Other BCAAs e.g. valine and isoleucine can be elevated too.

Molybdenum cofactor deficiency or isolated sulfite oxidase deficiency can also present with encephalopathy

and intractable seizures in the neonatal period. As the disease progresses, they have pyramidal signs, choreoathetosis and severe mental retardation. A characteristic lens dislocation may be presents in infancy. A low plasma uric acid is found in molybdenum cofactor deficiency. A positive urine sulfite dipstick can point towards this diagnosis, but is low in sensitivity and specificity. Urine amino acid analysis typically shows excretion of large amounts of sulfite, thiosulfate, S-sulfocysteine and cystine. The enzyme deficiency can be diagnosed via assays of cultured fibroblast or liver.

Glut-1 deficiency syndrome can also present with intractable seizures in the first week of life. This is due to a defect in the protein that transports glucose across the blood brain barrier. Diagnosis is suggested by a CSF: blood glucose ratio of <0.6. Confirmatory testing includes red blood cell glucose uptake studies and mutation analysis.¹⁰ Treatment involves a ketogenic diet to provide alternative fuel to the brain.

Vitamin-responsive seizures are another rare cause. Pyridoxine-dependent seizure can begin in the first week of life or even as early as in utero. These seizures are non-responsive to traditional anticonvulsants. These patients have a dramatic response to pyridoxine which is evident both clinically, as well as, on the electroencephalogram. Other similar vitamin responsive seizures include pyridoxal phosphate and folinic acid.¹¹

Conclusion

It is important to consider inborn errors of metabolism when faced with a neonate who is encephalopathic. Baseline investigations are important in streamlining the diagnostic

process and the need for more extensive and sometimes, expensive diagnostic tests. Early diagnosis and intervention is critical in determining the morbidity and mortality from such cases.

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