Neurology

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Journal reference:

1. Lefvert AK, Osterman PO. Newborn infants to myasthenic mothers: a clinical study and an investigation of acetylcholine receptor antibodies in 17 children. Neurology (Cleveland) 1983;33:133-8.

Textbook reference:

2. Moossy J. Vascular diseases of the spinal cord (chap 34). In: Baker AB, Baker LH, eds. Clinical neurology, vol 3. Hagerstown MD: Harper & Row, 1976:1-10.

Abbreviations of journal names are given in *Index Medicus.*

Mathematic formulas and equations that occupy more than 1 line of type should be avoided.

Letters to the Editor are welcome. They should be limited to two double-spaced pages.

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letters to the editor

Reye's syndrome and short-chain fatty acids

To the Editor: In measured plasma levels of short-chain fatty acids in Reye's syndrome, McArthur et al[1] found a significant increase only of propionic acid levels in patients with moderate or severe clinical signs, and of isovaleric acid concentrations in patients with moderate signs; isobutyric, n-butyric, n-valeric and caproic acid concentrations showed no elevation, but tended to values lower than those of controls. Of these six acids, increased levels of only isovaleric and propionic acids occur in disorders of biotin-dependent carboxylases. Isovaleric acid is elevated in cases of diminished activity of 3-methylcrotonyl-CoA carboxylase; propionic acid is elevated in propionyl-CoA carboxylase deficiency.[2] The most prominent finding[3] in a postmortem examination of mitochondrial liver enzymes in patients with Reye's syndrome was reduction of pyruvate carboxylase activity, another biotin-dependent carboxylase, and this could explain the lactic acidemia of Reye's syndrome.[1,4] We found a marked reduction of plasma levels of biotin (caused by intake of anticonvulsants) and elevation of biotin-dependent short-chain fatty acids in the urine of seizure patients.[5,6] Because Reye's syndrome is sometimes a fatal complication of anticonvulsant therapy,[7] the possible relation between biotin status or biotin-dependent carboxylases should be considered in investigations of Reye's syndrome.

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Jean-Pierre Bonjour, PhD
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References

1. McArthur B, Sarnaik AP, Mitchell RA. Short-chain fatty acids and encephalopathy of Reye's syndrome. Neurology (Cleveland) 1984;34:831-4.
2. Bonjour JP. Biotin-dependent enzymes in inborn errors of metabolism in humans. World Rev Nutr Diet 1981;38:1-88.
3. Robinson BH, Taylor J, Cutz E, Gall G. Reye's syndrome: preservation of mitochondrial enzymes in brain and muscle compared with liver. Pediatr Res 1978;12:1045-7.
4. Tonsgard JH, Huttenlocher PR, Thisted RA. Lactic acidemia in Reye's syndrome. Pediatrics 1982;69:64-9.

5. Krause KH. Biotin-Erniedrigung unter antiepileptischer Behandlung: Ein Beitrag zur möglichen Wirkungsweise von Antikonvulsiva. Freiburg: Hochschul Verlag, 1983.
6. Krause KH, Bonjour JP, Berlit P, Kochen W. Biotin status of epileptics. Ann NY Acad Sci 1984 (in press).
7. Jeavons PM. Hepatotoxicity of antiepileptic drugs. In: Oxley J, Janz D, Meinardi H, eds. Chronic toxicity of antiepileptic drugs. New York: Raven Press, 1983:1-45.

Reply from the Authors: Krause, Berlit, and Bonjour offer an interesting explanation for the origin of short-chain fatty acidemia in Reye's syndrome (RS). To our knowledge, plasma biotin levels have not been measured in Reye patients, and the possibility of drug-induced biotin deficiency cannot be excluded. Nevertheless, some clinical and biochemical findings seem to be inconsistent with this mechanism as the primary cause of Reye's syndrome.

Clinically manifest biotin deficiency is rare, reported with prolonged parenteral alimentation or excessive ingestion of raw egg white.[1,2] The typical manifestations (including seborrheic dermatitis, alopecia, and conjunctivitis) are slow to develop and respond promptly to biotin therapy. Conversely, Reye's encephalopathy is manifested by pernicious vomiting, behavior changes, and agitation that are sometimes followed by decorticate or decerebrate coma. Flaccid coma and death may result from brainstem compression due to intracranial hypertension.

Several chemical agents (including valproic acid) have been incriminated as causes of a "Reye-like syndrome." However, none of them has been documented as a cause of the salient ultrastructural, biochemical, and histochemical changes in liver that are characteristic of Reye's syndrome and which collectively define it as a distinct disease. In two patients with fatal hepatic failure after use of valproic acid, the liver injury differed from the lesion of RS on histopathologic examination.[3] Hepatic pyruvate carboxylase activity is decreased in RS, but the biotin-independent hepatic mitochondrial enzymes, such as glutamic dehydrogenase and monoamine oxidase, are also decreased.[4] These alterations are probably due to a general injury of hepatic mitochondria.

Given the fasted state of the RS patient before admission and the high rate of protein catabolism,[5] the relatively modest elevations of short-chain fatty acids would be expected.

Robert A. Mitchell, PhD
Brian McArthur, MS
Ashok P. Sarnaik, MB, BS
Detroit, MI

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1. Mock DM, DeLorimer AA, Liebman WM, Sweetman L, Baker H. Biotin deficiency: an unusual complication of parenteral alimentation. N Engl J Med 1981;304:820-3.
2. Van Lancker JL. Molecular and cellular mechanisms in disease. New York: Springer-Verlag, 1976.
3. Suchy FJ, Balistreri WF, Buchino JJ, et al. Acute hepatic failure associated with the use of sodium valproate. N Engl J Med 1979;300:962-6.
4. Mitchell RA, Ram ML, Arcinue EL, Chang CH. Comparison of cytosolic and mitochondrial hepatic enzyme alterations in Reye's syndrome. Pediatr Res 1980;14:1216-21.
5. Snodgrass PJ, DeLong GR. Urea cycle enzyme deficiencies and an increased nitrogen load producing hyperammonemia in Reye's syndrome. N Engl J Med 1976;294:855-60.