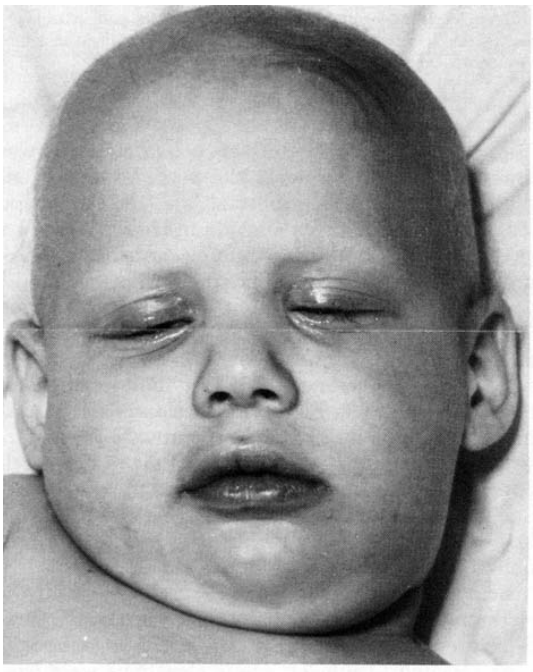
# Sick Kids with an Unusual Organic Aciduria

Case Study Problem No. 5 - Written by Harold B. White

**Page 2 - The Challenge**

One day a pediatrician presents your team with an especially puzzling pair of similar cases which she has never seen described in the literature. Although she respects your group's talents and certainly wants to help her patients, privately she is entertained by the idea that these cases will finally stump you. How, she asks, can a single enzyme defect cause the accumulation of the organic acids she observes?

## DESCRIPTION OF THE FIRST PATIENT



*The patient was a white female two years and nine months old, the product of a full-term pregnancy and delivery. At three months of age she began to have generalized seizures that occurred approximately 10 times per day and were unresponsive to phenobarbital. The seizures persisted and at 14 months an eczematoid rash and alopecia developed, progressing to involve the entire head, including eyebrows and eyelashes. At 16 months of age the patient was first noted to have metabolic acidosis with a serum bicarbonate less than 15 mmol per liter. By 21 months she had ataxia, severe enough to interfere with her ability to walk. At 22 months she was first noted to have an elevated concentration of lactic acid in plasma. At 31 months she had severe kerato-conjunctivitis requiring hospitalization. The patient's developmental progress was normal until seven months of age, when her development was delayed. From seven to 37 months her developmental age progressed by only 22 months. Throughout this period she received a normal diet and at no time was fed raw eggs. Her physical appearance at 31 months of age is shown in Figure 1. She was profoundly acidotic with plasma lactic acid concentration of 41 mg per deciliter(4.6 mmol per liter) and pyruvate concentration of 2.7 mg per deciliter (0.31 mmol per liter). She was irritable, somnolent, and in moderate distress, with marked alopecia, keratoconjunctivitis, and perioral stomatitis.* [Reprinted from the *New England Journal of Medicine* **304**:817-820 (1981).]

**How would you use the information provided above to seek a diagnosis?**

# DESCRIPTION OF THE SECOND PATIENT

The second patient was a two-year old boy whose profile of urinary organic acids (Table 1) was similar to those of patient 1. The values in the tables are the results of two consecutive 24 hour samples done twice - first at 21 months and then again at 23 months of age.

**Table 1 Urinary Excretion of Organic Acids (mol/mg creatinine) by Patient 2.**

| Item measured | 0-24 Hours | 24-48 Hours | 0-24 Hours | 24-48 Hours | Normal Values |
|---|---|---|---|---|---|
| Organic Acids<br>....3-Methylcrotonylglycine | 1.79 | 2.86 | 1.06 | 2.52 | <0.01 |
| ....3-Hydroxyisovaleric acid | 8.85 | 9.59 | 5.62 | 5.82 | <0.16 |
| ....3-Hydroxypropionic acid | 0.27 | 0.36 | 0.42 | 0.26 | <0.01 |
| ....Methylcitric acid | 0.28 | 0.31 | 0.27 | 0.20 | <0.01 |
| 24 Hour Urine Volume (ml) | 182 | 102 | 110 | 253 | |
| Creatinine (mg/ml) | 0.35 | 0.60 | 0.95 | 0.48 | |

**Postulate a *single* gene-enzymatic defect that could explain the presence of the various organic acids in the above table.**

**In the above cases, supplementation with a single substance reversed the symptoms and led to normal growth and development. What is the substance and how does it work?**