Glutaric Aciduria Type-1 (GA1) is an autosomal recessive disorder of amino acid metabolism, clinically characterized by progressive dystonia, dyskinesia, striatal degeneration (in particular, caudate and putamen), and the presence of macrocephaly common at birth. The disease characteristics are:

**Major clinical findings:**
- Dystonia, macrocephaly, episodic encephalopathy
- Other clinical findings may be present:
  - Muscular hypotonia, spasticity, mental retardation, ataxia, dysarthria, abasia, choreoathetosis, abnormal CT/MRI

**Routine laboratory findings:**
- Metabolic acidosis, hypoglycemia, ketosis, hepatopathy during encephalopathic episodes

**Special laboratory findings:**
- Increased glutarate, 3-hydroxyglutarate and glutaconate in urine, and increased glutaryl-carnitine in serum

The biochemical defect is in the metabolism of lysine, hydroxylysine, and tryptophan, due to deficiency of glutaryl-CoA dehydrogenase (see figure). A case with GA1 is presented below.

A two-year old Caucasian girl with history of fetal macrocephaly, hypotonia, and developmental delay was found to have significantly elevated glutaric, 3-hydroxyglutaric and glutaconic acids on urine organic acid analysis performed by gas chromatograph-mass spectrometry (GC-MS), consistent with the diagnosis of glutaric aciduria type-1 (GA1). Plasma acylcarnitine profile, done by tandem mass spectrometry, showed highly elevated glutaryl-carnitine confirming GA1 (see table below). It is noteworthy that the states that perform newborn screening by tandem mass spectrometry include GA1 screening.

**Laboratory findings in the case:**

| Urine* | Glutaric | 2280 (<6) |
| Glutaconic | 396 (<1) |
| 3-OH-Glutaring | 438 (<6) |

| Plasma$ | Glutaryl Carnitine | 1.73 (<0.07) |

*mmol/mol creatinine, $umol/l, reference ranges are shown in brackets.

Brain MRI showed typical findings of GA1, including widening of the Sylvian fissures, atrophy of the parietal temporal lobes, and increased signal intensity of the deep white matter, the basal ganglia, especially the putamen and to a lesser degree the globus pallidus.

Therapy with a protein restriction diet and carnitine supplementation was started.

During viral illnesses, correction of metabolic acidosis, hypoglycemia, and dehydration should be instituted to avoid irreversible dystonia and seizures. GA1 workup should be considered in non-hydrocephalic but macrocephalic newborns.
News from Immunology

IgG Antibodies Directed Against Tetanus Toxoid
by Charles Barnes, PhD

Tetanus (lock jaw) is an ancient disease caused by toxin of the bacterium *Clostridium tetani*. This organism can be found existing harmlessly in the animal and human intestinal tract. But, when placed in an anaerobic environment in the presence of something to alter the oxidation-reduction potential of the surroundings (puncture wound from a rusty nail), lethal tetanus toxin is produced. Tetanus toxin is one of the most poisonous substances known. One milligram can kill 100 million mice. Tetanus neurotoxin and botulism toxin produced by *Clostridium botulinum* are members of the clostridial neurotoxin family of proteins. These toxins have similar mechanisms of action in that they interfere with neurotransmission by blocking neurotransmitter release.

Deaths from tetanus in the US have been declining since 1940, as immunizations became common. During 1998-2000, an average of 43 cases of tetanus was reported annually. Eighteen percent of those cases were fatal and 75% of the deaths were among patients older than 60 years. No deaths occurred among those who were up-to-date with tetanus toxoid vaccination. Tetanus toxoid consists of inactivated tetanus toxin. It is available either by itself or in combination with other vaccines (DT or DPT).

Completion of a primary series of tetanus vaccinations will produce immunity to tetanus for at least 10 years in more that 95% of persons. Booster doses are recommended every 10 years. Although it is common to give tetanus toxoid booster to a wounded person, tetanus toxoid cannot act fast enough to give immunity to those who are not completely vaccinated. Tetanus immune globulin is a preparation of human antibodies directed against tetanus toxoid that can provide immediate immunity and may be given for tetanus prone wounds.

The Clinical Immunology Laboratory has the ability to measure human serum IgG antibody levels directed specifically against tetanus toxoid. The determination is by enzyme-linked immunosorbent assay using as reagents tetanus toxoid and tetanus immune globulin supplied by the pharmacy. There is no absolute or universal protective level of antibody.

The minimum level of neutralizing antibody in humans currently considered protective, 0.01 antitoxin unit/ml, is based on animal studies that correlated levels with symptoms or death. We set our protective level 10 times this value at 0.10 antitoxin units/ml of serum.

The determination of serum levels of tetanus specific IgG is sometimes used to determine if a child is protected against tetanus toxin, but more frequently, it is used to assess humoral immunity response to protein antigens. Typically, tetanus antibody levels are ordered in children whose humoral immunity response is suspect. If adequate levels of tetanus immune globulin are present, humoral immunity is considered to be adequate at least as far as protein antigens are concerned. If adequate levels of tetanus immune globulin are not present, the child is vaccinated with tetanus toxoid and antibody levels are again determined after four weeks. Typical responses demonstrate a one-log increase in measured tetanus-specific antibodies. Failure to achieve at least a doubling of tetanus- specific antibodies or failure to raise tetanus specific antibodies into the protective range indicates a potential problem with humoral immunity response.

CME Series
Sponsored by
Department of Pathology and Laboratory Medicine

Date: December 16, 2003
Time: 12:00 Noon
Location: Conference Room 2206.10 WT
Speaker: Dr. Spencer Kerly, Director of Pathology, PRL
Topic: The Regional Laboratory Alliance