Experience with 37 Infants with Tyrosinemia

J. LAROCHELLE, A. MORTEZAI, M. BELANGER, M. TREMBLAY, J. C. CLAVEAU and G. AUBIN, *Chicoutimi, Que.*

WE STUDIED all infants with cirrhosis seen in the Pediatric Department of l'Hôtel-Dieu St-Vallier, Chicoutimi, in the 11 years between 1954 and 1965, and were able to identify 37 with tyrosinemia. Nine were detected in 1965 alone because of a more systematic search.

All these infants were from the Saguenay-Lake St. John region of Quebec. Even if no immediate consanguinity was found, it is probable that there is a common hereditary basis, inasmuch as there is a high degree of inbreeding in that region. In fact, all the residents of the region are descendants of the original settlers of Baie St-Paul and La Malbaie. The 37 infants (21 girls and 16 boys) came from 26 families in which there have been 125 pregnancies. Certain details of the composition of these families are shown in Table IV.

TABLE IV.—FAMILY DATA ON 37 PATIENTS WITH TYROSINEMIA AND CIRRHOSIS OF THE LIVER

Total number of families	26
Pregnancies in the (26) families studied	125
Abortions and other deaths in the (26) families studied	29
Living children in the (26) families studied	61
Children affected by cirrhosis	37
Families having	
1 child affected by cirrhosis	19
2 children affected by cirrhosis	3
3 children affected by cirrhosis	4

The babies were products of full-term normal pregnancies and normal deliveries. The age at onset of the first symptoms of the disease varied from one to seven months, with a maximal frequency between two and four months. Most of the patients died in the same month that the disease was discovered.

CLINICAL FEATURES

The clinical features in these 37 infants with tyrosinemia are summarized in Table V and Fig. 2. General manifestations consisted of a rise in temperature and irritability, followed by lethargy, leading to coma in the terminal stage. A gastrointestinal syndrome was always present, characterized by anorexia, vomiting, diarrhea and abdominal distension. There was also early hepatomegaly with edema. Ascites and jaundice appeared late. A hemorrhagic syndrome occurred early and was often serious. We noted

TABLE V.—CLINICAL FEATURES IN 37 INFANTS WITH TYROSINEMIA

Manifestations:

General:
- Fever: 101° - 104° F.
- Irritability, lethargy, drowsiness

Gastrointestinal:
- Anorexia
- Vomiting
- Diarrhea
- Abdominal distension

Hepatic:
- Hepatosplenomegaly
- Edema
- Jaundice

Hemorrhagic:
- Melena-hematemesis
- Hematuria
- Ecchymoses—petechiae
- Epistaxis

Peculiar odour of the urine

hemorrhages of the digestive and urinary tracts, skin and mucous membranes, manifested by melena, hematuria, ecchymosis and epistaxis. The particular odour is a remarkable feature early in the course of the disease and was found in all cases where it was sought. The odour is evident after micturition, the urine smelling of methionine.

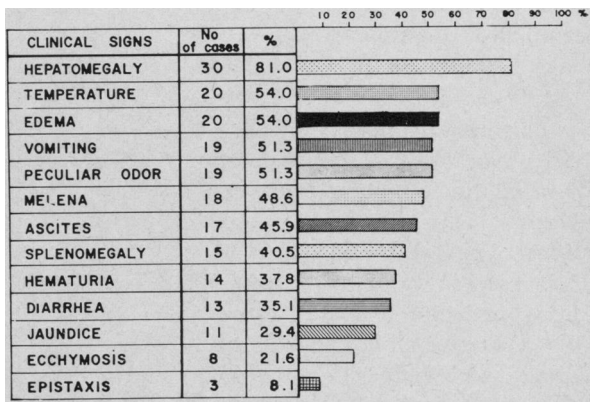

Fig. 2.—Relative frequency of clinical signs in tyrosinemia.

LABORATORY INVESTIGATIONS

Laboratory examination revealed normocytic anemia with hyperleukocytosis in all cases (Table VI). The platelets were slightly diminished in some, probably owing to hyper-

Canad. Med. Ass. J.
Oct. 28, 1967, vol. 97

TABLE VI.—LABORATORY FINDINGS IN TYROSINEMIA

Tests	Number of patients studied	Abnormal results	
Blood:			
Blood formula	37		
hemoglobin	37	Normocytic anemia	37
white cells	37	Hyperleukocytosis	37
platelets	31	Increased	8
Bleeding time	26		0
Coagulation time	26		0
Urine:			
Hematuria	35	Positive	14
Aminoaciduria	13		13
Millon reaction	8		8
Galactosuria	15		0
Pentosuria	3		1
Glycosuria	32		3
Hepatic investigation:			
Bilirubin	20	Increased	19
Alkaline phosphatase	14	Increased	10
Protein electrophoresis	28		28
Amino-acid (chromatogram)	9		9
Total cholesterol	20	Decreased	20
Esterified cholesterol	6	Decreased	6
SGOT	16	Increased	12
SGPT	16	Increased	11
Prothrombin time	27	Decreased	27
Ammonia	6	Increased	6
Kunkel's test	14	Increased	1
Thymol	22		0
Cephalin-cholesterol	13	Increased	12

splenism. The bleeding and coagulation times were always normal.

The blood glucose level was decreased in the 19 infants in whom it was determined. The values ranged between 40 and 70 mg. %. The hypoglycemia is probably due to an impairment of the hepatic gluconeogenesis.

Urinalysis revealed no proteinuria, but sometimes glycosuria. Tests for galactose and phenylketonuric acid were negative. A urinary amino-acid chromatogram was performed in 13 infants and showed a massive aminoaciduria. The form of the tracing was similar to the plasma chromogram. The Millon reaction showed that the levels of tyrosine and its derivatives were high — between 200 and 800 mg. %.

The hepatic tests showed a particular type of generalized dysfunction affecting both excretory and metabolic functions. The total bilirubin was increased in 19 of the 20 cases in which this test was done. The increase affected both the direct and indirect bilirubin. The total bilirubin never exceeded 8 mg. %. The alkaline phosphatase was normal or slightly elevated. The total cholesterol was normal. In the 28 patients studied, plasma protein electrophoresis showed marked changes, reflecting hypoproteinemia affecting both the albumin and the globulin.

The amino-acid chromatogram performed by an AutoAnalyser (Fig. 3) showed an important increase in all serum amino-acid levels. This amounted to from 3 to 15 times the normal values, except for valine, leucine and isoleucine, which remained within normal limits owing to their extrahepatic catabolism. However, the levels of phenylalanine, tyrosine and methionine rose to from 5 to 10 times the normal. The degree of elevation of methionine can serve as an index of the severity of the disease, as will be demonstrated later.

The total lipids were either normal or slightly decreased; however, the esterified cholesterol level was markedly decreased. The SGOT and SGPT transaminases were slightly increased, never exceeding 214 and 153 units, respectively. The blood ammonia level was always increased and the cephalin cholesterol flocculation tests were positive, but the Kunkel and thymol turbidity tests showed no abnormalities. The coagulation mechanism, on the other hand, was severely affected. The prothrombin level was markedly diminished, and was always between 0% and 40%.

The disease did not affect the blood urea, serum calcium, serum phosphorus levels, serum electrolytes, blood pH, or bicarbonate levels. The karyotypes done were normal. The Rh factor and blood group determinations of all the

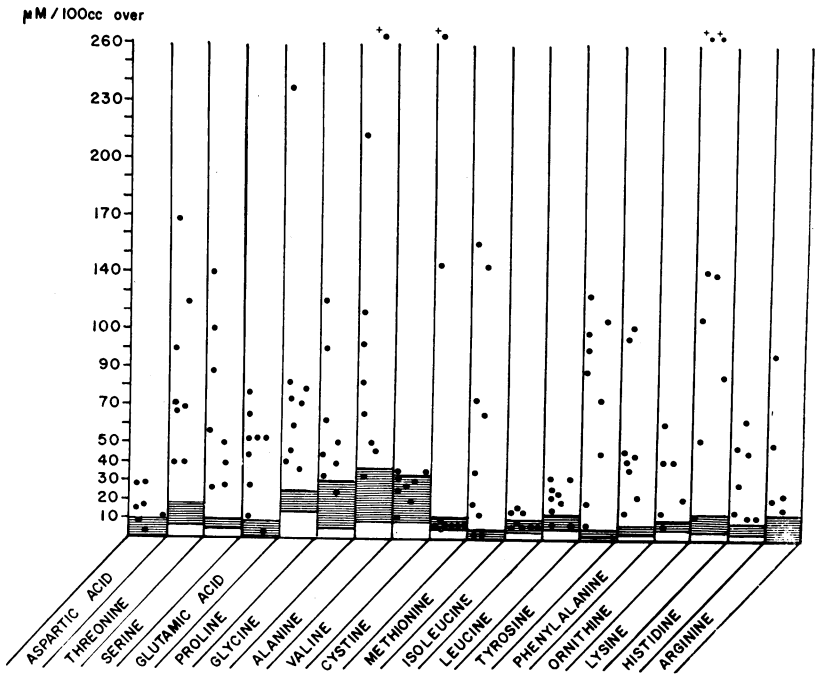

Fig. 3—Plasma amino-acid levels in nine infants.

babies and the mothers showed no incompatibility.

These 37 infants had early advanced or progressive cirrhosis, a complex renal tubular defect and, in some cases, a pancreatic impairment. The disease progresses rapidly to a fatal termination if not treated. In our view, it is due to an enzymatic block affecting tyrosine catabolism, as demonstrated by hypertyrosinemia and by increased urinary tyrosine and its derivatives.

The histoenzymatic study of four cases by Dr. La Du has confirmed a deficiency of pHPPA oxidase in the hepatic parenchyma.

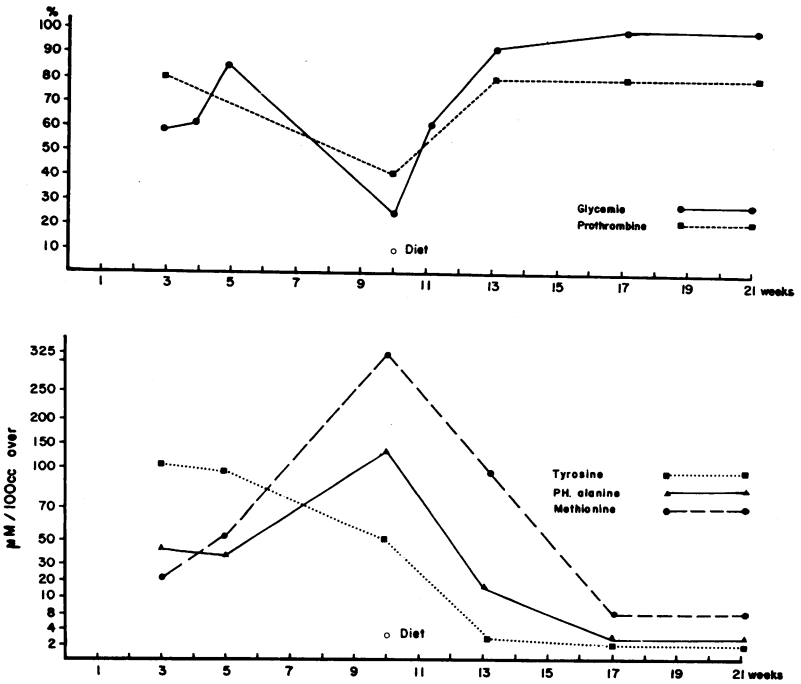

Fig. 4.—Glycemia, prothrombin time and plasma levels of tyrosine, phenylalanine and methionine before and after diet in patient N.G.

DISCUSSION

A new therapeutic approach to this serious metabolic defect seems possible, using a low tyrosine diet, as suggested to us by Dr. C. R. Scriver. In fact, two of our patients have been treated for several months using this diet, and the results seem very encouraging.

About a year ago, at the annual meeting of the Canadian Paediatric Society,[48] we reported 29 of these cases of cirrhosis in infants which we thought was linked to abnormal methionine production. At that time, most of the patients studied had very high levels of methionine in their blood, associated with a specific odour of the urine that could easily be compared to that of methionine. These findings suggested to us an error in the metabolism of this amino acid; an idea that was probably shared by others.

Later, Drs. A. Sass-Kortsak and C. R. Scriver drew our attention to the possibility of an error in tyrosine metabolism. This was confirmed by the histoenzymatic study carried out by Dr. B. N. La Du.

A few months ago, we obtained strong evidence that the hypermethioninemia is secondary to a defect in tyrosine metabolism. Baby N.G., whose sister had died earlier of the disease, came to the hospital at 3 weeks of age for a screening test. The child was asymptomatic at that time. However, her tyrosine and phenylalanine levels were elevated, but the methionine level was normal (Fig. 4). The infant was permitted to go untreated for a period of 10 weeks, inasmuch as the diagnosis was not completely assured. Without the diet, the methionine level rose markedly. After 10 weeks, we started her on a low tyrosine and phenylalanine diet. The blood level of these amines rapidly diminished, although the methionine level required a longer period of time to fall. Thus we are convinced that the defect is primarily one of tyrosine metabolism and that the hypermethioninemia is secondary to hepatic failure. We are equally certain that elevation of the other amino acids in the blood is also dependent upon liver dysfunction.

With the diet, the amino-acid levels, prothrombin time and glycemia all returned to normal. The child now appears happy and is progressing normally.

Perhaps we should now examine methods by which this disease may be discovered while we may yet treat it efficiently. In the families known to have had an infant with tyrosinemia we are now attempting to screen all newborns at 2 or 3 weeks of age. This screening test consists of blood and urine chromatograms, and a Millon reaction on 24-hour urines. At present, at l'Hôtel-Dieu St-Vallier de Chicoutimi, our biochemist, Dr. Belanger, routinely performs these urinary screening tests in all patients suspected of mental disease or metabolic disorders.

All the families have been advised that children born in the future might have tyrosinemia.

Canad. Med. Ass. J.
Oct. 28, 1967, vol. 97

We hope that in time we will be able to provide metabolic screening tests for all newborn infants in this region.

Recent progress in pediatrics and the understanding of the exact pathogenesis of this newly discovered inborn error of metabolism should permit us not only to make an early diagnosis, but also to treat this disorder efficiently. Although at this time we cannot reach definite conclusions, we hope that, with diet, children with this disease may be able to have the same advantages of treatment as those suffering from galactosemia and phenylketonuria.

ADDENDUM

We regret to report that the two patients who were on the diet died recently. The first one died at seven months with all the symptoms of a bulbar encephalitis. There was diffuse hepatic fibrosis, but no nodular cirrhosis. The second infant died at 3 months, soon after signs of hepatic insufficiency appeared. The liver, the pancreas and the kidneys all showed the changes associated with this disease.

While on the diet, these two patients were asymptomic and the laboratory tests remained normal until their deaths. Two additional patients are progressing normally with the diet. Seven other patients died almost immediately after being admitted to hospital.

Pathological Findings in Patients with Tyrosinemia

L. PRIVE, *Chicoutimi, Que.*

LIVER tissue was studied in 29 of the 37 infants from the Chicoutimi area described by Dr. Larochelle and his colleagues. Complete postmortem examination was carried out in 25 and liver biopsies in the four others. Except for generalized edema and signs of diffuse hemorrhage, the abnormal autopsy findings were usually limited to the liver and kidneys.

Grossly, the liver was slightly to moderately enlarged, rather yellowish, firmer than normal, and very faintly nodular. A variable number of small pale spots were discernible through the capsule and on the cut surfaces. The kidneys were enlarged, sometimes up to three times the normal weight. They were pale, soft and edematous, with poor architectural demarcations (Fig. 5).

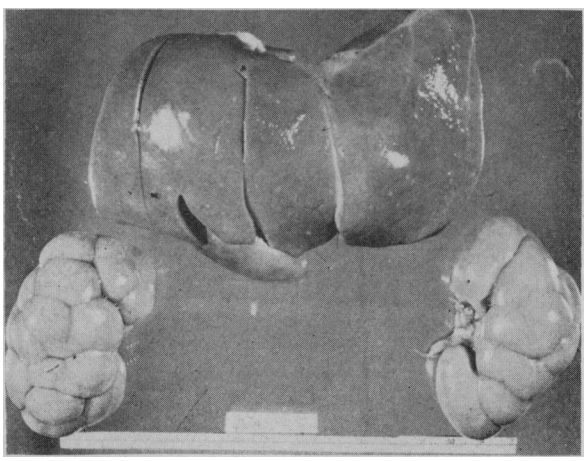

Fig. 5.—Gross aspect of liver and kidneys.

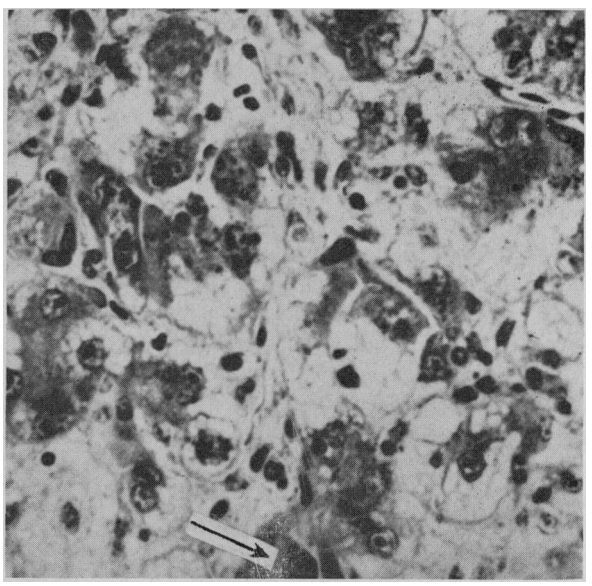

Fig. 6.—Liver: vacuolar degeneration of liver cells and infiltration, chiefly with monocytic inflammatory cells. Bile lake is visible at the bottom of the photograph. (× 400.)

Microscopically, the liver showed a diffuse and loose fibrosis, severely distorting the lobules but not destroying them completely. Associated with this fibrosis was a diffuse inflammatory infiltrate mostly composed of lymphocytes and monocytic cells. There was bile stasis, as evidenced by intralobular bile lakes. A great number of liver cells showed pyknosis and incomplete degeneration (Fig. 6). The cytoplasm of these cells contained numerous vacuoles, which on special staining proved to be fatty material. Histo-