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Encephalopathy and Fatty Degeneration of the Viscera in Childhood:

I. Review of Cases at The Hospital for Sick Children, Toronto (1954-1966)

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IN 1963, Reye, Morgan and Baral[1] of Australia reported a syndrome of encephalopathy and fatty liver occurring in children. This association had been previously described,[2-5] and subsequently cases have been reported from New Zealand,[6] Czechoslovakia,[7, 8] the United Kingdom,[9-12] South Africa[13] and the United States of America.[14-20] The admission to The Hospital for Sick Children, Toronto, of two siblings of a child with this condition led to the examination of the records of previous cases seen at this hospital during the past 15 years.

Cases were selected from the autopsy index by reviewing all those coded under "fatty liver", "encephalopathy of unknown origin" and "encephalitis, probably viral". Criteria for final selection were a typical clinical course (see below) and, at necropsy, a diffusely fatty liver with no associated histological evidence of encephalitis. A total of 21 cases satisfied these criteria and are included in the present study.

CLINICAL COURSE

The history and clinical course were fairly uniform in the 21 cases collected. A prodromal phase, usually of about four days, but occasionally lasting up to a week, was followed by a catastrophic event leading to unconsciousness and death in about one day. This prodromal phase often consisted of a mild upper respiratory or other poorly defined febrile illness. Vomiting was frequent in this period but neither the child's physician nor the parents thought that the child was seriously ill. The patients usually appeared to recover for a day or so but were brought to hospital because of focal or generalized convulsions, delirium or a quiet drift into coma.

These children usually were hyperventilating, suggesting salicylate intoxication and prompting an estimation of blood salicylates. As death approached, respirations became irregular and finally failed. Alterations in reflexes were variable. Muscle tone fluctuated between hypertonic and hypotonic, and many of the children when touched or stimulated assumed a decerebrate posture. No child showed signs of meningeal irritation. Nine children were delirious. Nine had generalized convulsions and three had focal seizures. In 15 cases the liver was palpable before death. Vomiting of coffee-ground material occurred in six cases.

Treatment, which included varying combinations of intravenous fluid infusions, antibiotics, steroids, vasopressors, sedatives, anticonvulsants, hypothermia and assisted ventilation, was supportive and ultimately futile.

Over 50% of the children were dead within 24 hours of admission to hospital. Of the six who survived longer than 30 hours, all but one required assisted ventilation.

LABORATORY DATA

Hypoglycemia, metabolic acidosis and respiratory alkalosis were frequently noted in these children. In 14 cases blood glucose estimations were available; eight of these were less than 50 mg. per 100 ml. and levels as low as 5 and 11 mg. per 100 ml. were recorded. In five cases the blood glucose was within the normal range. One child had a high level (227 mg. per 100 ml.), but before this determination her clinical condition had suggested hypoglycemia and she had received 50% glucose in distilled water intravenously. Cerebrospinal fluid glucose levels were measured in eight cases; three of these were less than 50 mg. per 100 ml. but most others were measured after the intravenous administration of glucose.

Ten of 17 children had a blood pH less than 7.4, the lowest being 7.30. The CO_2 content was always less than normal, and was less than 15 mEq. per litre in eight cases.

The white blood cell count was elevated in 15 of 16 cases, being above 20,000 cells per c.mm. in eight children, and ranging as high as 49,700 cells per c.mm. Differential cell count showed a neutrophilia. Urinary ketones were found in eight of nine cases tested.

Cerebrospinal fluid protein was not elevated in the seven cases where it was measured, but in two cases 20 to 40 lymphocytes per c.mm. and in three others between 5 and 10 cells were found.

Liver function tests were rarely performed, but in two children cephalin-cholesterol flocculation and thymol turbity were positive and

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their serum glutamic-oxaloacetic transaminase levels were 1400 and 700 units, respectively. The electroencephalographic records in seven cases were markedly and diffusely abnormal, but no specific diagnostic patterns were noted.

POSTMORTEM FINDINGS

Histological sections of brain showed edema. Very occasional neurones had anoxic changes. In a few cases small perivascular hemorrhages were present. In each of three cases, one section showed a single vessel surrounded by a cuff of lymphocytes. These were insufficient to warrant a morphologic diagnosis of viral encephalitis. Fat stains of frozen sections of brain showed occasional capillary endothelial cells containing oil-red-O-positive material but no fat emboli.

In all cases the liver was increased in weight, although generally not more than 10 to 15% above normal; the organ showed various shades of yellow. On microscopic examination diffuse fatty changes were seen throughout the lobule. The shape of the liver cells was maintained, the nucleus remaining centrally placed with the fat distributed in tiny droplets around it. Fat stains of frozen sections confirmed the intense fatty change in the liver and the distribution of the fat in multiple tiny droplets around the nucleus. Kupffer cells appeared more prominent than normal, and contained smudgy eosinophilic material and occasionally fat droplets. There was a slight inflammatory cell infiltrate in the portal tracts in three cases, and two of these showed occasional single necrotic liver cells adjacent to the portal tracts. The "piecemeal" necrosis of infectious hepatitis was never seen. A section of liver from one of the youngest children (5½ months) showed a few multinucleated giant cells resembling those seen in neonatal hepatitis. In another case (associated with chickenpox, where assisted ventilation and profound hypotension had lasted for eight days) there was bile stasis in the canaliculi.

In less than half the cases fat stains of frozen sections of the kidney were available. These showed tiny fat droplets in the basal portion of tubular epithelial cells, especially in the proximal convoluted tubules. Hematoxylin and eosin stains of kidney showed only pallor and minimal fine vacuolation of epithelial cells of the proximal convoluted tubules. In the few cases where fat stains of muscle and heart were available, mild fatty change of these tissues was present. Adrenal cortices were depleted of lipid in all but one child who had a recent infarct of the pituitary gland attributed to a long period of hypotension (this was the same patient who showed bile stasis in the liver).

Bronchopneumonia or pulmonary edema and focal hemorrhage were present in 10 cases. Small esophageal erosions or acute peptic ulcers of stomach or duodenum were found in six cases, and blood was present in the gastrointestinal tract in ten. Sections of pancreas were normal in all but two cases, in each of which a single duct was surrounded by polymorphonuclear leukocytes.

GENERAL FACTORS

Retrospective studies have many sources of error, and few conclusions may be drawn from a small series like this one. The disease affects both sexes (8 females and 13 males). Eight of the 21 children were aged 5 to 12 months, three were between 1 and 4 years, and the remaining 10 were 4 to 9½ years old. The first case of which we have record occurred in 1954 and the remaining 20 from 1958 to 1966, not more than four occurring in any one year. The majority of the cases occurred in the fall and winter months: seven in January to March, four in April to June, two in July to September, and eight in October to December. No geographic clustering of cases was evident.

Since 10 of the 13 children over 1 year of age had previously responded normally to one or more viral illnesses (rubella, mumps, chickenpox or measles) it is unlikely that they had an inborn defect in their ability to tolerate such infections. One 2½-year-old child had not had any of these diseases, and in two cases no information was available. Little can be inferred from the children under 1 year of age (seven of whom had had none of these diseases, while one had survived measles). None of the children had a history of being "sickly" or having an inordinate number of infections.

One child had a history of rheumatic fever seven months before death. Another 4½-year-old girl had suffered from the nephrotic syndrome and had been treated with corticosteroids, although none had been given for a year before her death. A third had scarlet fever two years before death, and a fourth had bronchitis and a questionable allergy to wool and cereals. All four of these children had had a normal response to one or more of the common viral diseases of childhood.

ASSOCIATION WITH VIRAL DISEASE

There was a background of viral illness or a suggestive history in three-quarters of the cases.

An older brother and sister of a 6½-year-old girl were admitted with infectious hepatitis 14 and 25 days, respectively, after her death (this

family prompted the present review). Viral cultures and virus antibody titres in this famly were not remarkable, but during his illness the brother showed a tenfold increase in the coxsackie A9 titre. The condition of both siblings improved and they were discharged to convalesce at home.

Three children were admitted four to five days after first developing a chicken-pox rash. One of these, a 3-year-old boy, was dead on admission to hospital. His 10-month-old brother was admitted on the same day with an illness which started with fever, vomiting, diarrhea and convulsions. For the next two to three days he was semicomatose and had a palpable liver. Liver function tests were abnormal. He gradually improved and was discharged 10 days later.

An older and a younger brother of a 5-year-old boy were sufficiently ill with a febrile condition to warrant admission to hospital within a day of his death.

Members of the family of a further five children had a "cold" or "upper respiratory infection". Two children who had not had mumps had a history of contact with mumps.

Viral antibody studies were done in few of the patients. Titres were always low for the particular antibodies tested and were generally not helpful because paired sera were not studied. Virus was not recovered from cultures of cerebrospinal fluid samples and postmortem tissues taken from six children, from cerebrospinal fluid alone from three children, or from postmortem tissue alone from an additional three children.

ASSOCIATION WITH TOXINS

Because of the rapid downhill clinical course and the evidence of severe liver disease, the possibility of ingestion of toxic substances has been considered. The parents of seven children in this series were specifically questioned but denied the possibility of ingestion of poisons. A high level of inorganic phosphorus was reported in one child by another laboratory. No history of exposure to phosphorus could be obtained, however, and clinical opinion was that the child was not suffering from phosphorus poisoning. Only three of the 21 patients were in the age range of 1 to 4 years, when accidental poisonings are most common. This is probably a fortuitous age distribution in this series.

Blood salicylate levels, measured in 10 children, were all less than 25 mg. per 100 ml. In seven cases the level was less than 20 mg., although in many instances the children had received salicylates to control fever for some hours before admission.

It is unlikely that the etiology of the fatty liver was iatrogenic, as no common single drug was administered to every child. Seventeen children received penicillin in some form, and nine of these were also given chloramphenicol. Only one child received tetracycline. Eleven were treated with adrenal corticosteroids after hospitalization. Paraldehyde was administered to 11 children to control seizures. A variety of other drugs was also used, but each drug was given to less than one-quarter of the patients.

Fifteen cases had negative lung and blood cultures at autopsy, and these together with the demonstration of negative blood cultures during life, would appear to exclude bacterial toxins.

DISCUSSION

The etiology of the syndrome is not clear. The most favoured theories postulate an overwhelming virus infection, a toxin, or a combination of factors which terminate in the same clinical and pathological picture.

The syndrome has been described in association with chickenpox[14-16, 21, 22] and infectious hepatitis,[4, 8] but five children in this series had survived chickenpox before their fatal illness. Virus isolations have been infrequent. Utian, Wagner and Sichel[13] reported isolating coxsackie A and a reovirus, while Golden and Duffell[19] found an echovirus, and Becroft[6] reported herpes simplex. Dvorackova, Vortel and Hroch[8] isolated adenovirus Type 3 from various tissues, including liver, at postmortem examination. In another case at this hospital (reported separately in Part II) influenza B virus was recovered from a liver biopsy and from various tissues at autopsy.

The significance of the history of contact with other viral diseases such as mumps, or association with viral illness in a family, is hard to assess. Although a virus may be involved, most of the cases in this series occurred in winter when mild viral illnesses are prevalent and probably a random group of children would show the same number of contacts. The rarity of virus isolations from these children makes it difficult to attribute the syndrome to a viral infection. The demonstration of an increasing viral antibody titre in surviving members of the family would strengthen the epidemiological evidence, but this was not tested in most of our cases. Hepatitis-encephalitis associated with reovirus can occur in humans,[23] but the changes described are not those seen in this syndrome. Chang, Geyer and Andrus[24] have reported isolation of a virus producing a lipogenic toxin.

Fatty changes in the liver and kidney have suggested a toxin, but only three positive toxicological studies of similar patients have been reported. Curry, Guttman and Price[2] found pteridines in the urine and Randolph *et al.*[17] demonstrated trace amounts of isopropyl alcohol.

Recently, Glasgow and Ferris[25] reported a study of a 4-year-old girl with the clinical picture described who died. Fatty liver was found at necropsy. Because the child lived in the vicinity of a car-spraying establishment, a detailed toxicological examination was performed, and isopropyl alcohol was found in the gastrojejunal contents by gas-liquid chromatography.

Reye, Morgan and Baral[1] pointed out the clinical similarity to, and the pathological differences of this syndrome from, the "vomiting sickness of Jamaica". That disorder results in hypoglycemia attributed to hypoglycins A and B, which are contained in the Ackes nut.[26, 27] Becroft[6] had drawn attention to aflatoxins—products of *Aspergillus flavus,* which are are known, experimentally at least, to produce fatty liver. The search for a toxic substance may have to move from the well-known and obvious poisons, like phosphorus and carbon tetrachloride, to fungal and vegetable poisons existing in foodstuffs, or to the complex chemicals such as insecticides now in domestic use.

A third possibility is that a viral infection may be required to trigger the syndrome in a child suffering from intoxication with (for example) a fungal or vegetable toxin. Finally, individual susceptibility or idiosyncrasy may be the cause. Perhaps the syndrome can be produced by several different agents. Whatever is postulated as the etiologic agent, it must explain not only why isolated deaths occur in a family (where presumably all the children are exposed to more or less the same environment), but also the relationship between the brain damage, hypoglycemia, acid-base imbalance and the fatty liver.

Usually the children had not eaten for several days before admission and were vomiting and ketotic, both of which tend to lower the blood sugar.[28] Mortimer and Lepow[16] have attributed the hypoglycemia occurring in their cases of varicella to the ingestion of salicylates. Limbeck *et al.*[29] have described several cases of hypoglycemia apparently resulting from extreme sensitivity to salicylates. If salicylates were the cause of the hypoglycemia, it is difficult to understand why this syndrome was not recognized and reported in greater numbers earlier than the 1960's. In this series blood glucose levels of 11 mg. per 100 ml. were associated with blood salicylate levels of 10.2 mg. and 7.6 mg. per 100 ml., respectively. Severe liver disease can cause hypoglycemia, but the degree of disturbance of liver function tests and the lack of necrosis in that organ make it difficult, short of a specific block in an enzyme system, to attribute the hypoglycemia to liver disease alone.

The brain damage could also result from hypoglycemia, but it must be emphasized that low blood sugars were not recorded in every case.

The children were acidotic and hyperventilating at a rate which would seem excessive for the degree of metabolic acidosis. Simpson[9] has suggested that the hyperventilation may be of central origin.

In the absence of liver biopsy and liver function tests, retrospective diagnosis in surviving cases is difficult and speculative. Survivors have been reported,[1] some with permanent cerebral damage.[13, 15, 16]

The etiology and pathogenesis are not clear, and therefore the most advantageous immediate course must be to pursue intensive investigation. Because of the rapidly fatal nature of the condition, a pre-established protocol for investigation is called for. Becroft[6] has suggested the following:

1. Examination of the patient's environment for toxins, immediately rather than retrospectively, with particular attention to the possibility of toxins in apparently innocuous foods and medicines.
2. Further toxicological investigations, including analysis for fungal products, and examination of the urine for the fluorescent material described by Curry, Guttman and Price.[2]
3. Further viral studies by all available techniques.
4. Chemical analyses of the liver and serum lipids, including estimations of serum lipoproteins.
5. Studies of liver enzymes, particularly those concerned with carbohydrate metabolism, preferably of biopsy rather than necropsy material.
6. Estimations during the acute stage of serum levels of adrenal corticoids, insulin and growth hormone.

To this, could be added:

7. Serial estimations of liver function, blood glucose and blood insulin studies, done on the same sample of blood and the results interpreted in relation to the amount of glucose being given intravenously.
8. Estimation of serum proteins, with fractionation of the immunoglobulins.
9. Determination of interferon levels.
10. Family studies with respect to associated illness, liver function and change in viral antibody titres, with follow-up to discover illnesses

manifested after the death of the index case in a family.

11. Inquiry into any dietary likes or dislikes of the children in the hope of explaining the isolated occurrence of these cases in a family.

12. Recording of the socioeconomic status, dietary habits and chemicals in use in the household in question.

At necropsy:

13. Assay of brain, liver and peripheral muscle for lipids and glycogen.

14. Study of pancreas for α and β cells.

15. Virus studies of individual organs.

Summary The clinical and pathological features of encephalopathy and fatty liver occurring in 21 children have been reviewed. The clinical picture was of a mild prodromal illness, frequently an upper respiratory infection lasting several days, followed by vomiting. The children then rapidly became unconscious and died, three-quarters of them in 24 to 30 hours. Laboratory investigation revealed hypoglycemia, mild metabolic acidosis, respiratory alkalosis and disturbed liver function. Necropsy showed cerebral edema and anoxic neuronal changes. There was marked diffuse fatty change in the liver and fat was present in the kidney tubules. The clinical, biochemical and pathologic features were not specific.

The association of the syndrome with chickenpox in three cases, with infectious hepatitis in other family members in one case, and with mild viral illness in the family in a quarter of the cases, was noted. Although there was an epidemiological association with viral disease, virus could not be isolated from these patients, making it difficult to establish the connection.

Lack of a history of exposure to toxins and lack of toxicological determinations did not exclude the possible etiological role of toxins. The possibility that several factors combine to cause the syndrome is suggested. A plan for investigation of future cases is outlined.

Because hypoglycemia alone could cause the brain damage, it should, when present, be treated vigorously in children suffering from any acute encephalopathy.

Résumé L'auteur passe en revue les cas de 21 enfants ayant souffert d'encéphalopathie et de dégénérescence graisseuse du foie et en analyse les caractéristiques cliniques et pathologiques. Le tableau clinique comportait d'abord des prodromes bénins, se manifestant souvent par une infection des voies respiratoires supérieures d'une durée de quelques jours, puis par du vomissement. A ce moment, les enfants devenaient rapidement inconscients et mouraient, les trois-quarts dans un délai de 24 à 30 heures. Les analyses de laboratoire révélaient de l'hypoglycémie, une légère acidose métabolique, une alcalose respiratoire et des fonctions hépatiques troublées. A la nécropsie, on notait un édème cérébral et la présence de lipides dans les tubes urinaires. Les caractéristiques cliniques, biochimiques et pathologiques n'étaient pas spécifiques.

On a constaté que le syndrome coïncidait, dans trois cas, avec la varicelle, dans un autre cas, avec une hépatite infectieuse ayant atteint d'autres membres de la famille et, dans 25% des cas, avec une maladie virale bénigne frappant la famille. Bien qu'il aît été incontestable qu'il existait une association épidémiologique avec une maladie virale, on n'a pu isoler de virus chez ces malades, ce qui a rendu difficile l'identification d'un facteur étiologique.

L'absence de renseignements sur les contacts avec des toxines et le manque de déterminations toxicologiques n'ont pas permis d'exclure le rôle étiologique possible des toxines. L'auteur estime, pour sa part, qu'il faudrait incriminer plusieurs facteurs pour la genèse du syndrome. Il propose un plan d'études des futurs cas.

Etant donné que la seule hypoglycémie risque de provoquer une lésion cérébrale, cette anomalie éventuelle devrait être traitée énergiquement chez tout enfant souffrant d'une encéphalopathie aiguë.

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