# Encephalopathy and Fatty Degeneration of the Viscera (Reye's Syndrome)*

Report of a Case and Brief Review of the Literature

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In 1963 a new syndrome was described in Australia by Reye et al based on the association of encephalopathy with severe fatty degeneration of the liver, kidneys and other organs.[1] The symptoms presented were fever, vomiting, convulsions leading to stupor, and coma. Although most of the reported cases have been fatal, some patients have recovered without further effects. Post-mortem studies have shown remarkable similarities in the histopathologic findings, except for minor variations in the details. Up to date, cases have been reported from South Africa,[2] Czechoslovakia,[3] the United States[4-5] and New Zealand.[6] In the recent review of the literature made by Randolph and Gelfman, they were able to collect 84 cases, and added to these two siblings who recovered completely. The cause of Reye's syndrome still remains obscure, but it would be worthwhile considering it in patients with acute progressive encephalopathy without any known explanation. More studies of future cases might prove valuable in understanding the etiology.

The purpose of this article is to present a case with the clinical and pathological findings of Reye's syndrome, which has not been previously reported from Turkey.

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*Case Report*

Y. K. (65/50987), a 12-month-old boy, was admitted to Hacettepe Children's Hospital on April 2nd, 1965. His chief complaints were fever, diarrhea, vomiting, coughing and somnolance. Mild diarrhea had started two weeks previously, later fever and coughing developed, and in the last two days the diarrhea had increased in severity with continued coughing and vomiting. The patient was the second child of the family, and his mother had an uncomplicated pregnancy until seven months, at which time she gave birth spontaneously after a trauma. The weight and length of the baby were not recorded, but according to the parents he had a low birthweight and was hospitalized. He gained weight, and after his return home cow's milk and liquid food were given. For the last two months juices from the family's food had been successfully added to his diet. He was able to sit at the age of six months, and his teeth appeared at 11 months. Consanguinity was found between the parents, who were first cousins, and the other three-year-old sibling was in good health.

Physical examination revealed a temperature of 37 C, pulse rate 148 per minute and respiration 48 per minute. His weight and length were 4,600 gm and 65 cm respectively. The head circumference was 40.5 cm and that of the chest 39 cm.

The patient was comatose, responding only to painful stimuli, and the chief findings besides this were irregularity of respiration, general spasticity, but without meningeal signs, and sluggish pupillary reaction to light. The deep tendon reflexes were increased, and the Babinsky signs were positive bilaterally. The liver was palpable three cm below the right costal margin, but examination of the other organs did not reveal any significant findings.

*Laboratory Examination*: Hb was 9.2 gr/100 ml, and the white blood cell count was 7,000 per 1 mm3 with a differential count of 68 per cent neutrophils, 31 per cent lymphocytes and one monocyte. Urinalysis showed a trace of albumin, one plus positivity of the Sulkowitch test, and occasional granular cylinders. Lumbar puncture pressure was not recorded. Clear spinal fluid containing 44 mgm/100 ml protein and 25 mgm/100 ml sugar was obtained, but a smear this revealed no cells or bacteria. Blood $CO_2$ was 20.97 mEq/Lt, that of Cl 100 mEq/ Lt, and PPD was negative. Blood and urine culture for bacteria yielded no growth.

The patient received sustaining treatment, and since a tentative diagnosis of tuberculous meningitis was made, antituberculous treatment was added. The comatous condition and irregularity of the patient's respi-

ration continued, and the severity of this general condition remained the same; the child expired two days after hospitalization.

*Post-Mortem Examination*

In view of his premature delivery, the patient's growth and development appeared to be within the normal limits except for slight malnutrition. No jaundice was detected, and the pleural, peritoneal and pericardial cavities contained no excess fluid. The lungs revealed sparse petechiae on the pleural surfaces, but no consolidation was found. The liver weighted 250 gr (the average normal weight being 185 gr) and showed diffuse yellow discoloration. The gall bladder and extrahepatic bile ducts showed no abnormality. Both kidneys had a similar appearance, with a well-preserved shape, and their combined weight was 60 gm (the average normal weight being 30 gm). The capsule, striped uniformly with easily visible pale cortices and with cortico-medullary demarcation on the cut surfaces, was clear. No dilation of the calyces or the pelvis was seen.

In the brain the leptomeninges were thin and transparent with engorged vessels and occasional petechial hemorrhages; the cerebral and cerebellar hemispheres were symmetrical, the gyri were flattened and the sulci narrowed. The cerebellar tonsils appeared swollen, but coning was not present. Coronal sections of the brain and spinal cord revealed that there was little congestion, and gross examination of the other viscera appeared normal.

*Microscopic Examination*: A section of the liver stained with hematoxylin and eosin showed an enlarge lobular architecture with diffuse vacuolizations of various sizes. Minimal round cell infiltration in the portal spaces were also seen (Figure 1). Frozen sections of the liver, stained with Scharlach R, were fat positive (Figure 2).

Sections of the kidneys stained with hematoxylin and eosin showed unremarkable glomeruli and the interstitial tissue. The proximal convoluted tubuli contained vacuoles in the cytoplasm adjacent to the basement membrane. Frozen sections of the kidneys stained with Scharlach R for vacuoles in the tubuli were positive (Figure 3).

Sections of the brain were examined from the cerebral and cerebellar cortices, basal ganglia, hippocampus, mid-brain, pons and spinal cord at various levels. Except for the edema, no inflammation, cellular changes or necrosis were seen. A frozen section, similarly stained for fat, showed fatty droplets in the endothelial cell of the capillaries and the tissue adjacent to it (Figure 4).

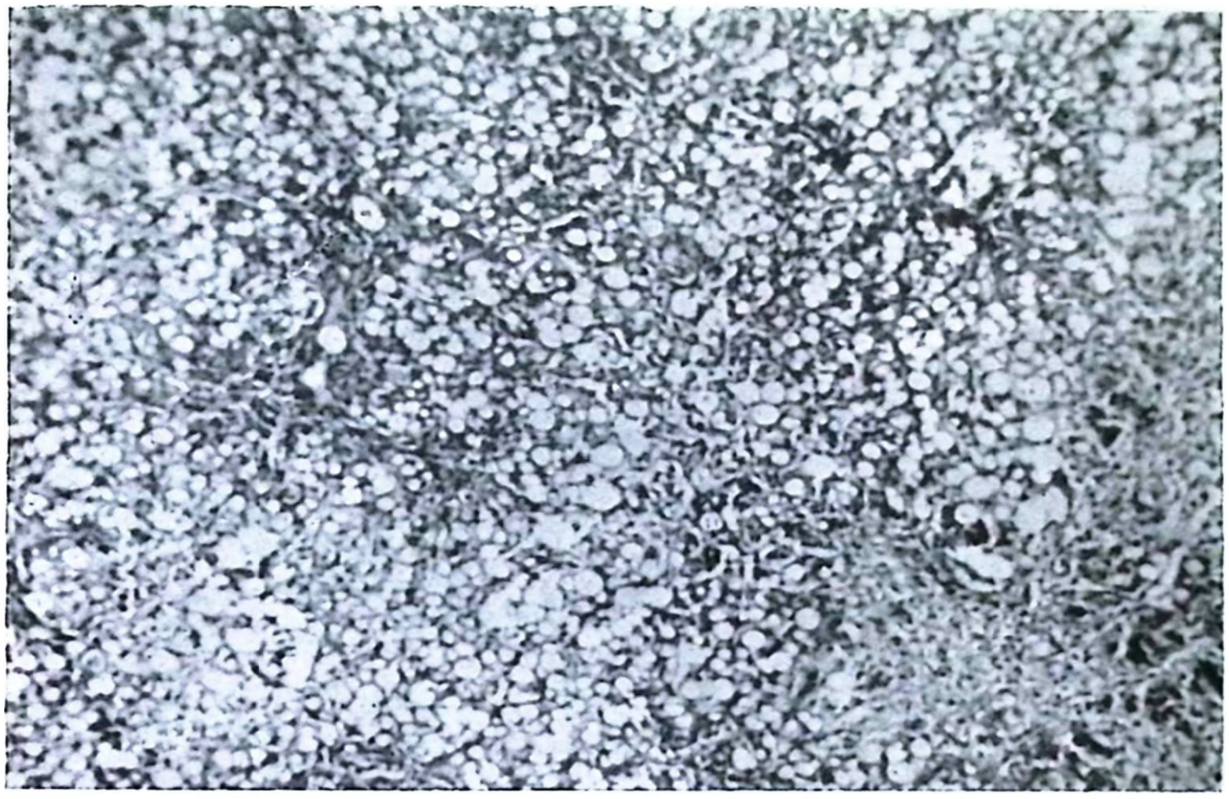

**Figure** 1. Section of the liver stained with H+E, showing round empty vacuoles in the hepatic cells, and some round cell infiltration in the portal spaces (X 180).

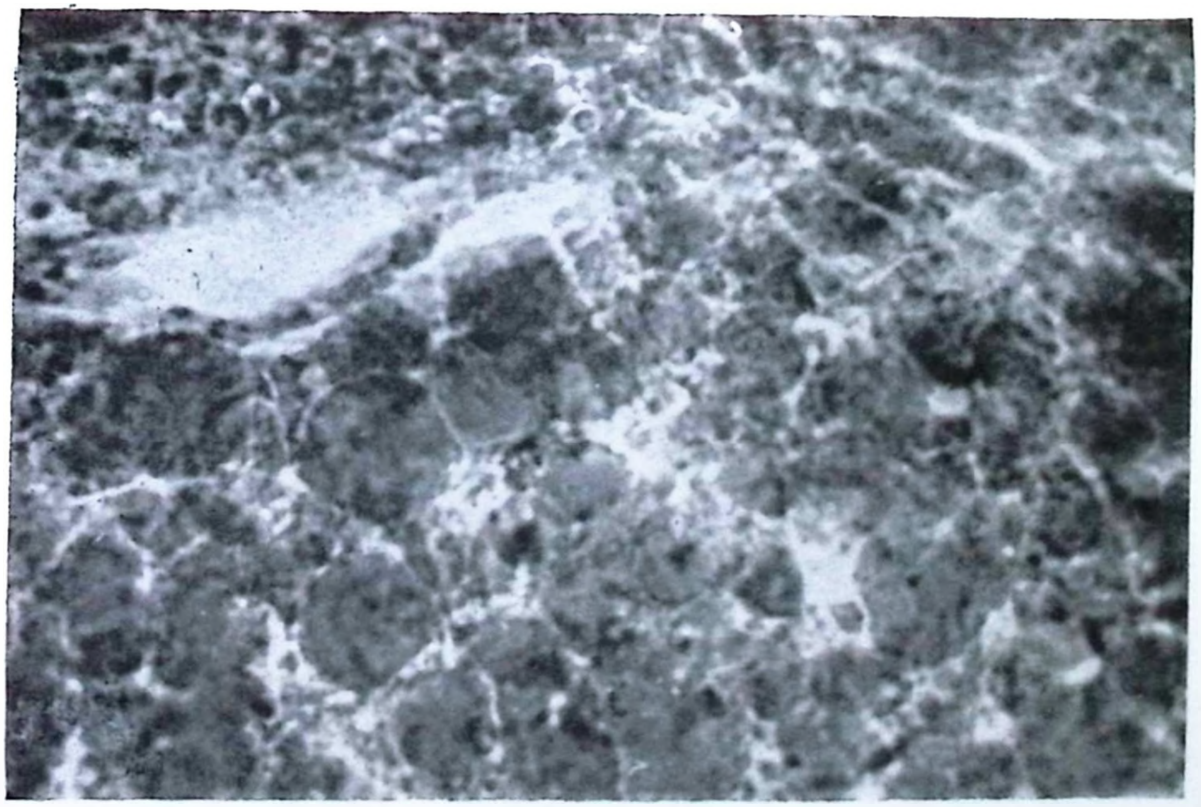

**Figure** 2. Frozen section of the liver stained with Scharlach R: Dark droplets represent presence of sudanophilic material in the hepatic cells (X 250)

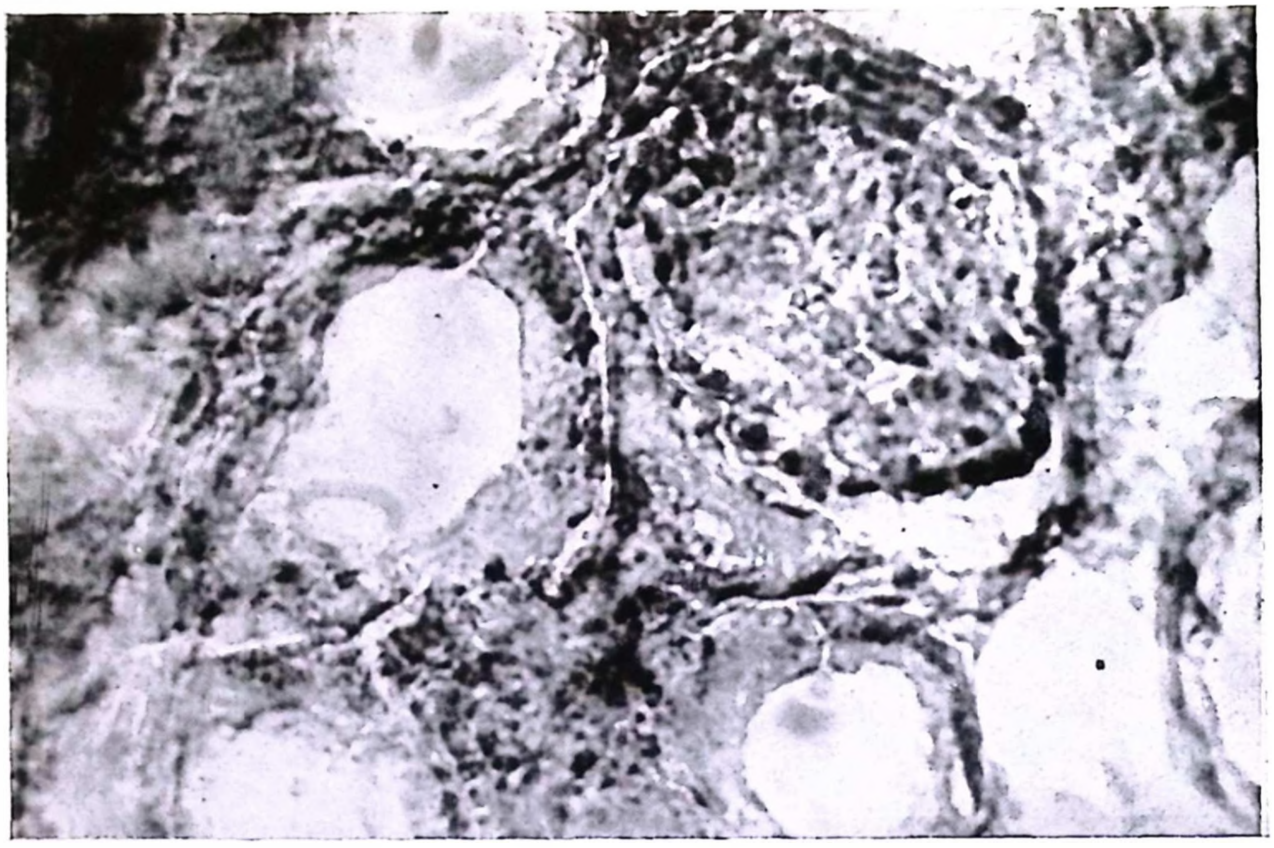

**Figure 3.** Frozen section of kidney stained with Scharlach R. showing presence of fat droplet in the epithelial cells of the proxymal convoluted tubules which are located basally. (X 250).

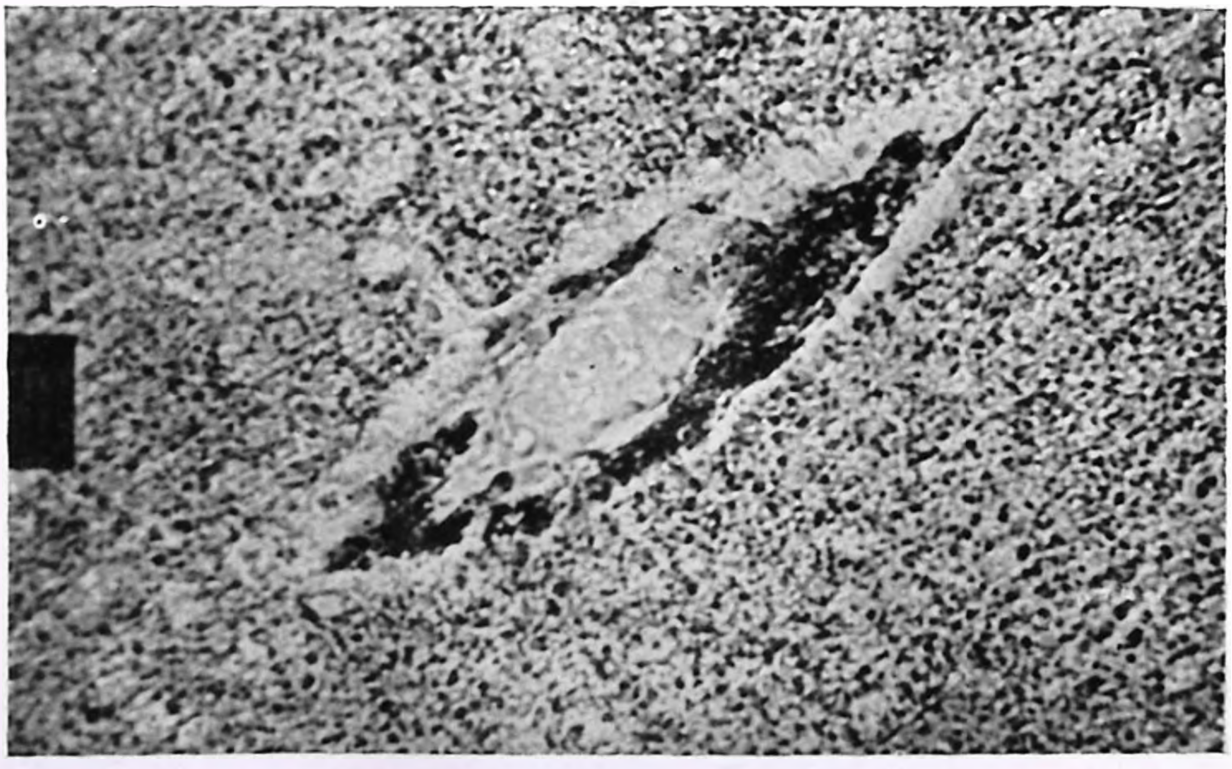

**Figure 4.** Frozen section of brain showing dark droplets representing sudanophilic material around the capillary.

Sections of the lung showed focal minimal bronchopneumonic infiltration, and subpleural petechial hemorrhage.

Sections of the myocardium similarly stained were negative. Post-mortem cultures from the blood, spinal fluid and the lungs for tuberculous bacilli were negative.

*Review of the Literature and Discussion*

After clinical and pathological studies of 21 children seen between the years 1951 and 1962, Reye et al[1] in 1963 described a syndrome of encephalopathy and fatty degeneration of the viscera. Two-thirds of the patients were less than two years old, the youngest being five months old, and the oldest eight and a half years old. Fourteen of these were female, and seven were male.

In all cases the syndrome began with upper respiratory infections, and later was suddenly aggravated with vomiting and encephalopathy. Tonic spasms were frequent, and the patients had vomiting, convulsions and coma, leading to death.

Outside the central nervous system the significant findings in 12 cases were rapid and irregular respiration, and markedly enlarged liver. All the patients had low glucose levels in the spinal fluid, and the blood sugar level in six out of nine cases was clearly shown to be below 50 mgr/100 ml. Slightly raised levels of BUN were thought to be a result of secondary dehydration. SGOT and SGPT levels were 106–1170 and 155–1200 Karmen units respectively.

Post-mortem examinations were made in 17 cases; however, pathologic findings were non-specific and showed remarkable uniformity. The brains were grossly swollen, and the livers were edematous and uniformly yellow. The kidneys had swollen cortices with pale cut surfaces.

Microscopic examination showed the liver to have fatty degeneration without hepatic necrosis or significant inflammation, and the kidney showed fatty vacuoles in the proximal tubuli and Henle's tubuli.

Sections of the brain showed neuronal and glial swelling, but no inflammatory reactions or degeneration. Fatty droplets appeared in the endothelium of the capillaries. In the early cases encephalitis or septicemia were thought to exist, but post-mortem studies did not confirm this impression. The authors noted hypoglycemia in their patients, but, in spite of high doses of glucose given intravenously the clinical picture remained the same.

After the first publication of the syndrome, new case reports appears in the literature.[2-8] In 1967 Bradford[8] reported a case, and this, together with a collection of all the others in the literature, showed that 69 out of 83 ended fatally, and post mortem studies were done on all of them. Fourteen patients were still alive, one of whom was not followed up; neurological defects remained in three cases, but recoveries from this syndrome have been rapid. A summary of the clinical findings is as follows: fever, diarrhea, vomiting, convulsions, hepatomegaly, distrubed pupillary reactions to light, increased muscular tonicity, occasional tetanic spasms, and abnormal plantar reflexes.

*Significant Laboratory findings*: About half of the patients showed low levels of blood and spinal fluid sugar. Of one third of the cases in which liver function tests were done, 14 showed abnormalities. Only six patients had EEG, all of whom showed abnormal findings. Post-mortem studies revealed brain swelling in 63 cases, fatty degeneration of the liver in all of them, focal hepatic necrosis in 15, mild portal mononuclear cell infiltrations in 15, fatty degeneration of the renal tubuli in 36, and bronchopneumonia in 13.

The etiology of Reye's syndrome is unknown. In some cases virus isolations such as Coxsackie and Reo viruses,[2] ECHO virus[4] and adeno type viruses[3] were reported. One case associated with chickenpox was also reported,[10] but Becroft[6] failed to isolate any virus from three cases studied. In 1968 Randolph and Kranwinkel[7] reported a case of two siblings who recovered completely, suggesting the value of serum transaminase level determination.

An etiology of toxic agents was also reported, with isopropyl alcohol in the tissue,[5] and another case an abnormal amount of pteridine in the urine was reported.[11] Fatty liver was also seen after intravenous administration of high doses of tetracycline.[12]

These studies in the literature are still far from clear about the etiology of Reye's syndrome. In our case both the clinical and specific postmortem studies were consistent with the syndrome; blood sugar determination was not done, but the spinal fluid sugar was 25 mgr/100 ml and the absence of histopathologic findings of hypoglycemia in the brain sections suggested that the patient did not have hypoglycemic brain damage.[11 13] The patient had a low degree of malnutrition, but since he was born prematurely, we felt that the role of malnutrition in this case was negligible.[14] Apart from the fatty changes in the liver, the findings in the kidneys and brain cannot easily be explained by malnutrition, and we therefore believed that this could only be a case of Reye's syndrome. The clinico-pathologic studies of patients with hepatic coma and hepato-len-

ticular degeneration suggest a relation between the brain and the liver as in Reye's syndrome, which affirmed itself once more in our patient. We also think, as the literature suggests, that in cases of encephalopathy the condition of the liver should be studied more closely.

*Summary*

A case of acute encephalopathy associated with diarrhea and vomiting is reported. Clinical and pathological studies confirmed this to be Reye's syndrome, and we believe this is the first case reported from Turkey. A brief review of the literature is also presented.

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