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SUBACUTE NECROTIZING ENCEPHALOPATHY (LEIGH SYNDROME): REPORT OF TWO JUVENILE CASES WITH FATAL OUTCOME*

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The clinical and pathological findings of two children diagnosed on autopsy with subacute necrotizing encephalopathy (SNE) are presented. One of the patients was a previously healthy 12-year-old boy with a rapid clinical course and fatal outcome. The second case was a mentally retarded 13-year-old girl with a positive family history of neurological disease and progressive deterioration.

Brain edema, bilaterally symmetric gray-brown areas of spongy degeneration and cavity formation were present in the basal ganglia in both cases. A small cavity was noted in the right inferior olive in Case 2. Mamillary bodies were spared in both cases macroscopically and microscopically.

Microscopic sections of the involved areas and the periaqueductal region in Case 2 exhibited variable degrees of necrosis, spongiosis with a striking proliferation, and dilatation of the capillaries. Similar changes were noted in the cerebral cortex of Case 1. Microglial and astrocytic proliferation with some loss of myelin were also noted. The neurons, although reduced in number, were frequently preserved within the lesions.

To our knowledge, only three patients over two years old have been reported in the literature with an acute clinical course and a fatal outcome. Case 1 is the fourth such case. *Key words: subacute necrotizing encephalo (myelo) pathy, Leigh syndrome, mitochondrial cytopathy.*

Subacute necrotizing encephalopathy or encephalomyelopathy (SNE) or Leigh syndrome is a rare degenerative disease of the central nervous system (CNS) associated with various biochemical defects and considerable clinical variability[1-6].

An autosomal recessive mode of inheritance has been suggested, and the onset is usually during infancy or early childhood[1-7]. However, in the sporadic or X-linked form, juvenile and adult cases have also been reported[2,6-13]. Recently, maternally inherited Leigh syndrome in two siblings was presented by Ciafaloni et al[14]. The

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clinical course is variable; although the affected patients usually die in the first few years after diagnosis, a rapidly fatal course, spontaneous remission, chronic evolution, a relapsing form and survival beyond three decades have also been documented[4,8,9,15,16].

Clinical manifestations at the onset include, in order of frequency: feeding problems; motor retardation; hypotonia; ocular signs and symptoms; mental retardation; seizures; respiratory problems; cerebellar, pyramidal and extrapyramidal signs; and coma[4].

The characteristic pathologic findings are necrotizing lesions most commonly found in the tegmentum of the midbrain, pons, medulla and basal ganglia with a symmetrical distribution. The lesions usually destroy both the gray and white matter, and gray-brown discolorations or cystic softenings can be observed on macroscopic examination. The histopathological changes consist of spongy necrosis with microglial and astrocytic reactions and prominent vascular proliferation[1,2,4-18].

Since the first description of this syndrome by Dennis Leigh[1] in 1951, more than 200 cases have been reported in the literature[4]. Although several defects of oxidative metabolism have been causally related to this entity, the definitive diagnosis still requires pathologic examination[3,4]. In a recent survey of the literature, van Erven et al[4] found 173 cases of pathologically proven Leigh syndrome.

We recently studied two children diagnosed on autopsy with lesions of the brain characteristic of this disease. These are the first cases seen in our Pediatric Pathology Department in the past twenty years. One patient was a previously healthy student with a sudden onset of the disease and a rapidly fatal outcome. To our knowledge, only three other patients over two years in age with an acute clinical course and fatal outcome are documented in the literature[6,8,9]. This report describes the clinical and pathological findings of the two cases seen in our department.

Case Reports

Case 1

A 12-year-old boy was admitted to a local hospital with a five-day history of constipation and difficulty urinating. After admission he became unable to walk and spoke incoherently. He was referred to Hacettepe Children's Hospital upon progressive obtundation. There was no history of exposure to drugs, chemical agents or animals. The developmental history was unremarkable. He was the sixth child of consanguineous parents. There was no family history of neurologic disease.

Physical examination on admission revealed a disoriented child. He cried intermittently and withdrew his lower extremities upon painful stimuli. Vital signs were normal; weight and height were in the tenth percentile. Pupils were bilaterally equal in size and reactive to light. The optic fundi were normal. Cranial nerve functions, muscle bulk and strength were intact. The lower extremities were spastic. Tendon reflexes were obtainable. There was sustained clonus of both ankles, and his Babinski sign was bilaterally positive. Meningeal signs were negative. The remainder of the physical examination was unremarkable.

Urinalysis, complete blood count, blood chemistry profile and pseudocholinesterase levels were within normal limits. Blood ammonia was 73 μg / dl (N: 70-120). Serum lactate was 4.5 mg / dl (N: 10-14) and pyruvate was 1 mg / dl (N: 0.5-1). Serologic tests for Salmonella and Brucella were negative. A lumbar puncture yielded clear, colorless, acellular cerebrospinal fluid (CSF) with normal glucose and protein contents; a culture yielded no microorganism. An X-ray film of the chest was normal. A cranial computed tomographic examination (CT) revealed bilateral radiolucent areas in the basal ganglia and scattered radiolucent regions in the frontal and parietal lobes. A second cranial CT scan performed five days after admission showed bilateral narrowing of the cortical sulci and ventricular systems. An electroencephalogram displayed irregular background activity with centroparietal focal slow waves.

The patient's condition rapidly deteriorated, and bilateral papilledema, anisocoria and bradycardia developed. Intravenous dexamethasone and mannitol were administered. Intravenous acyclovir was initiated for a tentative diagnosis of Herpes simplex encephalitis. Mechanical respiratory assistance was required for apnea and cyanosis. The patient died on the seventh day of admission despite intensive care. An autopsy was performed.

Case 2

A 13-year-old girl was brought to Hacettepe Children's Hospital with loss of consciousness. Generalized weakness and stupor of three days duration and vomiting following a minor head trauma one day prior to admission were noted.

She was the first child of distantly related parents. She was born at term after a complicated delivery. Her developmental milestones were delayed. A tentative diagnosis of choreathetoic cerebral palsy due to anoxic birth was made at nine years of age at Hacettepe University Pediatric Neurology Unit. Internal squint, rigidity of the extremities and right optic atrophy were noted at that time while serum and urinary amino acid levels and cranial CT were normal. She attended a special school for the mentally retarded. Degenerative CNS disease was considered at ten years of age. She was unable to walk without assistance, and her speech deteriorated.

Her 10-year-old brother was described as moderately mentally retarded. Several cousins of both the mother and father had histories of mental retardation, motor deterioration, and life expectancies of 25-30 years.

Physical examination on admission revealed a comatose child with irregular breathing who did not respond to painful stimuli. Cutis marmoratus and cyanosis were present. Pupils were slowly reactive to light; right optic atrophy and left papilledema were noted. Right facial nerve paresis was present. The extremities were spastic, and patellar tendon reflexes were unobtainable. Meningeal signs were negative.

The patient was resuscitated and mechanically ventilated in the Intensive Care Unit. However, she died within ten minutes of admission and laboratory investigations could not be done. An autopsy was performed.

Pathological Findings :

Both patients' major pathological findings present on autopsy were localized to the CNS. Brain edema and bilateral cerebellar tonsillar herniation were present in both cases.

Coronal sections of the cerebral hemispheres disclosed bilaterally symmetrical gray-brown areas of spongy degeneration with some cavity formation in the basal ganglia of both patients. The putamen and caudate nuclei were particularly affected (Fig. 1). Few small hemorrhagic discolorations were present in the gray matter of the cerebral cortex and rostral pontine in Case 1. A small cavity was noted in the right inferior olive in Case 2.

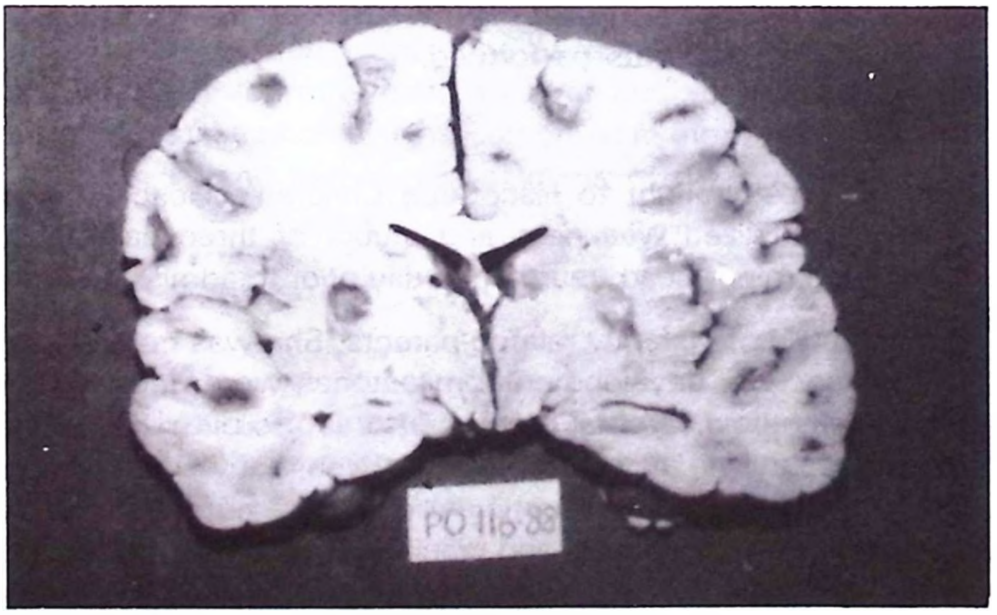

Fig. 1: Case 1: Coronal section of the cerebral hemisphere showing symmetrical spongy necrosis and cavity formation in the basal ganglia.

Microscopic Findings :

Case 1 : Sections of the basal ganglia exhibited varying degrees of necrosis, cystic degeneration and spongiosis with capillary proliferation (Fig. 2). In some sections of the cerebral cortex, spongiosis and proliferation of capillaries were also noted (Fig. 3). The hemorrhagic areas showed congested vessels surrounded by small recent hemorrhages. No changes were seen in the sections of the pons, medulla oblongata, periaqueductal region, mamillary bodies and spinal cord.

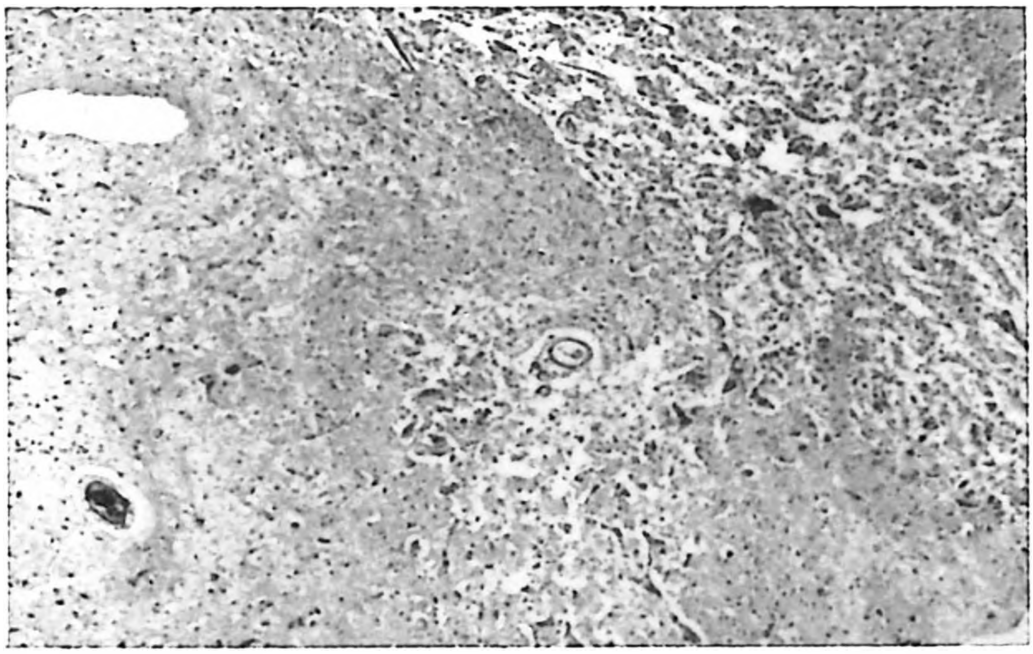

Fig. 2: Case 1: Necrotic areas in the basal ganglia. (HE, x 13).

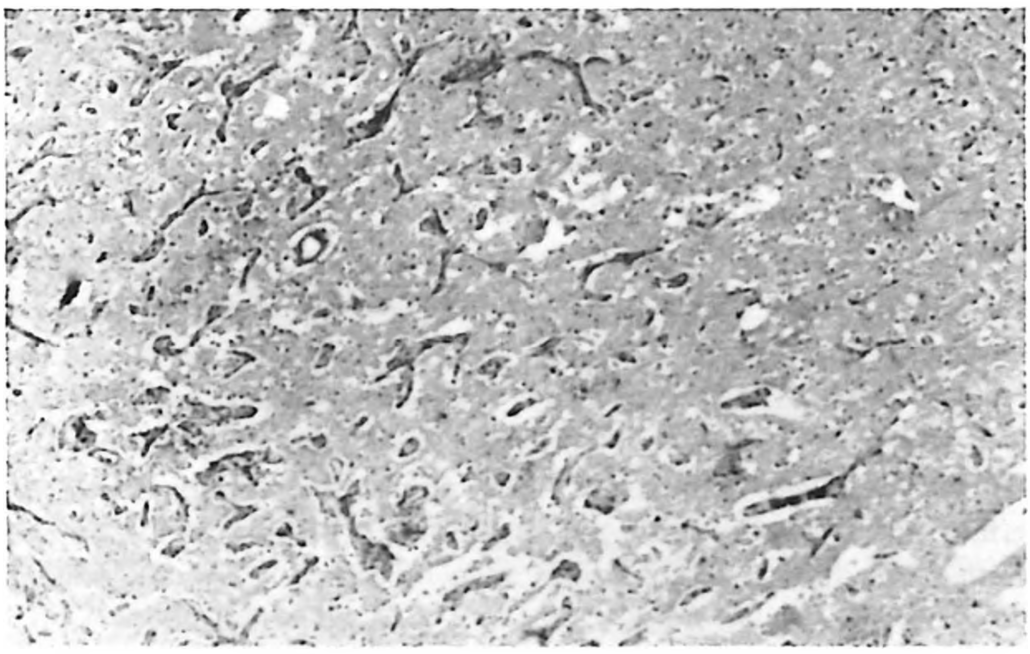

Fig. 3: Case 1: Cerebral cortex lesion showing marked proliferation of the capillaries and spongy degeneration. (HE, x 13).

Case 2 : Basal ganglia showed histopathological findings similar to those of Case 1. The lesions in the periaqueductal region were symmetrical and butterfly-like, and showed striking capillary proliferation and dilatation (Fig. 4). Rarefaction and cystic disintegration of the nervous parenchyma was detected in the right inferior olive. Brain edema was more prominent than in Case 1, and separations between the molecular and granular layers of both the cerebral and cerebellar cortex were noted. Slight vacuolization and loss of myelin was observed in the optic chiasma. No pathological changes were present in the spinal cord and mamillary bodies.

The neurons, although reduced in number, were frequently preserved within the lesions; microglial and astrocytic proliferation with some loss of myelin was also detected in both patients.

Fig. 4: Case 2: Periaqueductal lesion showing prominent vascular proliferation and dilatation. (HE, x 13).

Discussion

Subacute necrotizing encephalopathy (SNE) is a distinct pathological entity with variable clinical presentations[1-6]. Case 1 was a previously healthy child with an abrupt onset of neurological symptoms. Only three cases with an acute clinical course and rapid fatal outcome in children over two years of age have been reported in the literature[6,8,9]. Case 1 is the fourth such case. Case 2 presented with a history of developmental delay, psychomotor retardation and progressive deterioration. The family history was also suggestive of degenerative CNS disease.

The topography of the lesions within the brain tissue and the characteristic macroscopic and microscopic pathological findings of both children are consistent

with and supportive of the diagnosis of SNE. Case 1 had cerebral cortex and basal ganglia involvement. The cortical form of SNE has been reported in the literature[18]. Lesions can also occur in the spinal cord in 74% of patients; however, spinal cord involvement was not detected in our cases[4].

Because of the existence of hemorrhagic petechial areas in Case 1 and the resemblance of histopathological findings to SNE, a differential diagnosis was made with Wernicke's encephalopathy, a CNS disorder due to thiamine dificiency[2,19]. However, neither mamillary bodies nor hypothalamic involvement, most commonly seen in Wernicke's disease, was present[2,7,11]. In some cases of SNE, mamillary body involvement has been reported, and small hemorrhages have also been described[2,5,6,12,13,17].

Diverse biochemical causes have been proposed for the etiology of SNE[2-5]. In recent years, deficiency of pyruvate carboxylase (PC) or pyruvate dehydrogenase complex (PDHc), defective activation of PDHc and defects of the respiratory chain, such as cytochrome c oxidase complex I (reduced nicotinamide-adenine dinucleotide-coenzyme Q reductase) and succinate oxidation have been found to be associated with this disease[2-5]. These enzymes and the respiratory chain are located in the mitochondria, and their deficiencies cause a disturbance in energy metabolism. Thus, SNE is now accepted to be one of the mitochondrial cytopathies[4]. Recently, Ciafaloni et al[14] demonstrated a point mutation at nucleotide 8993 in the adenosinetriphosphatase-6, gene of mitochondrial DNA in the tissues of two half-sisters and their mother.

A disturbance of pyruvate metabolism or a deficiency of the respiratory chain often leads to elevated lactate and pyruvate levels in serum, CSF and urine. Determinations of the levels of lactate and pyruvate in body fluids are therefore of utmost importance in patients suspected of having SNE[4]. However, normal levels have also been described[7,15]. The serum lactate and pyruvate levels were normal in Case 1, while the CSF and urine levels of lactate and pyruvate were not determined. Unfortunately, no biochemical investigations could be done in Case 2.

A recent report by Baumgartner et al[5] of a child with laryngeal stridor, progressive neurologic deterioration, and death at 21 months of age has demonstrated biotinidase deficiency as a cause of SNE. The authors speculated that chronic lactate accumulation in the brain due to metabolic abnormalities may be responsible for the specific neuropathologic lesions in SNE. Lactate has been shown to be toxic to the brain and may be involved in neovascularization[20]. The specific and symmetrical distribution of the CNS lesions in the diencephalon and brain stem may be due to a selective local susceptibility of these structures to metabolic accumulation.

Hypertrophic cardiomyopathy associated with SNE has also been demonstrated on autopsy in some cases[21]; however, cardiomyopathy was not noted in our patients.

In a number of SNE patients, it is possible to demonstrate cerebral lesions on CT scan and magnetic resonance imaging (MRI). The most consistent findings are bilateral radiolucent or hypodense lesions in the basal ganglia, usually localized in the putamen[22]. Bilateral, symmetrical, low-density areas in the thalamus, throughout the midbrain, adjacent to the fourth ventricle and scattered throughout the cerebral cortex, have also been reported. retrospectively, the CT findings in Case 1 are consistent with these descriptions. Medina et al[23] recently reported MRI findings of nine patients with SNE, and emphasized a pattern of symmetrical hyperintense lesions on T2 weighted images involving the basal ganglia and brain stem with predominant involvement of the putamen as highly specific for SNE.

Despite all recent developments, the definitive diagnosis of SNE still rests on pathologic findings. However, specific attention to the signs and symptoms, genetic transmission, disturbances in energy metabolism and bilateral hypodense areas in the basal ganglia region on CT or MRI may lead to a clinical diagnosis in this syndrome.

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