Subacute necrotizing encephalomyelopathy (Leigh’s disease) in adults clinically diagnosed as multiple sclerosis

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A report is made on two women, aged 32 and 40 years respectively who died with subacute necrotizing encephalomyelopathy (adult form of Leigh’s disease). These two patients were incorrectly diagnosed clinically to have multiple sclerosis because of diversified neurologic manifestations affecting the visual, motor, sensory, and autonomic systems. The course of ailment lasted about 10 years in case 1, and 1 year and 10 months in case 2. A review of 15 cases of the adult form of Leigh’s disease, including these two patients, disclosed that clinically the malady showed psychomotor regression and brainstem dysfunction. The clinical diagnosis is confirmed by demonstrating symmetrical abnormalities in the basal ganglions on computed tomographic brain scan or magnetic resonance imaging. Pathologically, subacute necrotizing encephalomyelopathy is manifested by irregularly defined lesions in the basal ganglions, thalamus, brainstem, and spinal cord. These lesions are often bilateral and symmetrical, and contain proliferating small blood vessels with endothelial hyperplasia as well as relatively intact neurons. The etiology, pathogenesis, and appropriate treatment of Leigh’s disease remain to be elucidated.

Key words: Subacute necrotizing encephalomyelopathy, Leigh’s disease, Multiple sclerosis.

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สำราย ช่วงโรคติ, วิจัย สถานศึกษา, สุภิญยา เลิศถลิ่ง, เนโคظهชิน เอนเซช่าโสมัยโภชนาธิค รองเนียบพลัง (โรคของลิ่ง) ในผู้ใหญ่ที่ได้รับการวินิจฉัยทางคลินิกว่าเป็นเม็ดติเปิดคลอดโรลซิ. จุฬาลงกรณ์วิทยา-
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ได้รวบรวมผู้ป่วยหญิงไทย 2 ราย อายุ 32 และ 40 ปี ตามลำดับ ป่วยด้วยโรคเนโคظهชิน เอน-
เซช่าโสมัยโภชนาธิค รองเนียบพลัง ซึ่งได้รับการวินิจฉัยทางคลินิกว่าเป็นเม็ดติเปิดคลอดโรลซิ.
ผู้ป่วยที่ 1 รับประทานยาหลังปรับด้าน 10 ปี ระยะที่ 1 และ 1 ปี 10 เดือน ระยะที่ 2. การตรวจพยาธิสภาพ-
ที่เข้าถึงแก่โรคของลิ่ง 2 ราย ได้พบแนวทางการทั่วไปของผู้ป่วยโรลซินได้ในผู้หญิง 15 ราย
รวมที่ผู้ป่วย 2 รายที่รายงาน ณ ที่นี่ด้วย.

โรคของลิ่งจะแสดงอาการทางคลินิกที่สำคัญ คือการเสี่ยงมีอาการของร้องไห้และร่างกาย.
และ
การทดสอบในหน้าที่ของก้านสมอง ซึ่งทำให้ได้รับการยืนยันในการตรวจพบโรคที่มีเกิดขึ้นที่กองที่
น้ำคิดลิ่งของสมองและก้านสมอง ตัวรู้โดยเครื่องคอมพิวเตอร์ (CT) และ/หรือ MRI ก็อาจวินิจฉัย
โรคได้อาจที่ผู้ป่วยมีชีวิต.

ส่วนการทำการวิจัยที่จะพบโรลซินที่ประกอบด้วยการนำบายาของสมองสำหรับประกอบเป็น
นำคลอคลิก ดาโนส ก้านสมอง และ/หรือใดสินหลัง ซึ่งมักเป็นที่ 2 ซึ่งรวมไปกับการออกมาย้นของ
คลอคลิกของคลอคลิกและเอ็นไซคลิค กันโรลซินที่ออก_Part.1 โรลซิน และการปล่อยพยาธิสภาพใน
แบบมีสูตรเรียง

เนื่องจากโรคของลิ่งอาจมีอาการยาที่ผู้ป่วยไม่ได้
หลาย ๆ รูปแบบ เพราะโรคเกิดหลาย ๆ แห่งในระบบประสาท ซึ่งอาจทำให้เกิดอาการทางคลินิกว่า
เป็นเม็ดติเปิดคลอดโรลซิ. จึงควรต้องแยกกันได้.

สาเหตุ ทฤษฎีก้านเนื้อ และการรักษาที่เหมาะสม สำหรับโรคของลิ่งไม่เป็นที่ทราบกันดี.

สำราย ช่วงโรคติ, วิจัย สถานศึกษา, สุภิญยา เลิศถลิ่ง, เนโคظهชิน เอนเซช่าโ somaINE รองเนียบพลัง
(โรคของลิ่ง) ในผู้ใหญ่ที่ได้รับการวินิจฉัยทางคลินิกว่าเป็นเม็ดติเปิดคลอดโรลซิ.
Multiple (disseminated) sclerosis is generally acknowledged as extremely rare in Thailand. The Thai physician, nevertheless, has repeatedly attempted to make the clinical diagnosis of this disease. However, it is difficult to be certain of the clinical diagnosis of multiple sclerosis when there is no pathological confirmation. At Chulalongkorn Hospital, a general hospital of about 1,370 beds in Bangkok, only a single postmortem proven case of multiple sclerosis has been found in more than 30 years(1) indicating the true rarity of this malady. Two patients recorded here have also been clinically diagnosed to have had multiple sclerosis. But the postmortem findings in these two cases show that they did not have multiple sclerosis, but are indeed examples of subacute necrotizing encephalomyelopathy in adult patients (adult form of Leigh’s disease).(2-14)

Case reports

Case 1.

A 32-year-old nun was hospitalized because of progressive weakness in all limbs. Ten years earlier, she had been hospitalized because of bilaterally blurred vision. This symptom progressed slowly and she was informed to have degenerated optic nerves.

Five years later, she began to develop weakness in all limbs but still could walk.

One year ago, she had occasional headaches without nausea and vomiting.

Three weeks prior to hospitalization, she had headaches and difficulty in respiration. Two weeks prior to admission, numbness ensued at the distal parts of the hands and feet. Ten days prior to admission, weakness of all extremities became more severe. She entered a provincial hospital where she was found to have visual field defects, moderate weakness of the muscles in all limbs, and two plus deep tendon reflexes. Her consciousness was good. Cerebellar sign and stiff neck were absent. A leucocyte count showed 7,100 cells/mm³ with 77% neutrophils and 23% lymphocytes.

A lumbar puncture revealed 99 lymphocytes/mm³ 20 mg/100 ml of protein, and 66 mg/100 ml of glucose in the cerebrospinal fluid (CSF). She was transferred to Chulalongkorn Hospital a week later.

On admission here, her body temperature was 39.3°C, pulse rate 100/min, respiratory rate 32/min, and blood pressure 120/80 mmHg. The patient was conscious. Each pupil, 3 mm in diameter, was reactive to light. The visual acuity remained at finger count at 1 foot. There was impaired function of the seventh and twelfth cranial nerves. The other remaining cranial nerves were intact. Motor power was absent in all extremities. Pain and touch sensations were absent. There was no plantar response in Babinski’s maneuver. The ankle clonus was negative. Per rectal examination revealed loose sphincter tone. Detected throughout the lungs were medium to coarse crepitations.

Hemoglobin was 10.8 to 12 gm/100 ml and leukocyte counts revealed 8,200 to 15,800 cells/mm³ with 84 to 85% neutrophils, 13 to 16% lymphocytes, and 0 to 2% monocytes. A urinalysis disclosed a trace of protein, 5 to 10 leucocytes/high power field (HPF), numerous yeast cells/HPF, and few fungal filaments/HPF. Blood chemical studies revealed 141 to 159 mg/100 ml of sugar, 10 to 20 mg/100 ml of BUN, 1.2 to 2.0 mg/100 ml of uric acid, 123 to 135 mEq/L of sodium, 3.8 to 5.5 mEq/L of potassium 87 to 97 mEq/L of chloride, and 14 to 28 mEq/L of carbon dioxide.

The first lumbar puncture, 1 day after hospitalization, revealed opening and closing pressures to be 220 and 170 mm of water, respectively. The clear CSF contained 130 lymphocytes/mm³, 90 mg/100 ml of protein, and 61 mg/100 ml of sugar (blood sugar was 100 mg/100 ml). VDRL of CSF was negative. The second lumbar puncture, 10 days after hospitalization, showed 30 mg/100 ml of protein and 52 mg/100 ml of sugar (blood sugar was 141 mg/100 ml). Stain for acid-fast bacilli of the CSF sediment was negative.

A sputum culture exhibited heavy growth of Pseudomonas aeruginosa. A urine culture showed growth of Escherichia coli and yeast cells.

A computerized tomographic (CT) scan of the brain disclosed a lesion of low density in the right thalamus. A CT scan of the spinal cord showed a homogeneous and dense intramedullary lesion at the cervical region (Fig. 1). A myelogram showed an enlarged cervical segment of the spinal cord from C5 to C7.
Figure 1. (Case 1). CT scan of brain and spinal cord.
(A) CT scan of brain in horizontal plane shows small areas of decreased density in the thalamus on the right side.
(B & C) Intrathecal contrast-enhanced CT of the spinal cord in sagittal plane (B) and coronal plane (C) demonstrate enlargement of the cervical segment.

The treatment consisted of the administration of antibiotics (penicillin and gentamycin), antituberculous drugs, (INH and rifampicin), steroid, and other supportive measures. The patient had fever (38° to 41°C) and fluctuated blood pressure (60/30 and 140/90 mmHg). The respiration became laborious and this eventually required artificial oxygenation. She died 15 days after hospitalization. The total course of illness was about 10 years. The clinical impression was multiple sclerosis.

Postmortem Examination
The autopsy findings included bilateral bronchopneumonia and acute cystitis. A 1,330-gm brain showed thin and clear leptomeninges, and thin optic nerves with opaque sheaths. Coronal sections of the brain revealed necrotic foci in the thalamic nuclei, right temporal lobe (Fig. 2), right cerebral peduncle, and bilateral substantia nigra. Each necrotic zone was about 1.5 cm in diameter. The mammillary bodies were intact (Fig. 2), as was the hypothalamus. There was also necrosis of the mesencephalon and pons, as well as the periaqueductal gray matter.

Figure 2. (Case 1). Lesion of brain.
(A) Coronal section shows hemorrhagic spots, especially in bilateral centrum semiovale and thalami. An arrow points toward a necrotic focus in the right temporal lobe.
(B) Higher magnification of the necrotic region is shown (left arrow). Note intact mammillary bodies (right arrow). The scale is 1 cm in length.
The cervical segment of the spinal cord was soft, friable, and swollen (Fig. 3). The rest of the spinal cord was unremarkable.

**Figure 3.** (Case 1). Lesion of brain and spinal cord.
(A) Midbrain and cerebellum show necrotic zone in the right side of the former (arrow).
(B) Cervical segment of the spinal cord displays necrosis (arrow).

Tissues in this case, as well as in the other instance, were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin (H & E). Luxol-fast blue stain for myelin sheath and Gomori’s stain for reticulin fibers were also done. Frozen sections with oil-red-O stains on formalin-fixed tissue were also conducted to detect lipid.

Microscopically, the following alterations were encountered in the central nervous system (CNS), namely necrosis and status spongiosus of neuropil, vascular proliferation and endothelial hyperplasia, infiltration of microglia, gliosis, and relatively preserved neurons. These pathologic changes were similar in the brain (Fig. 4) and spinal cord (Fig. 5). It was unfortunate that the optic nerves were lost in the routine processing of tissue; hence, the pathologic changes is them could not be described.

The pathologic diagnosis of the CNS lesions was subacute necrotizing encephalomyelopathy (Leigh’s disease) in an adult woman.
Figure 4. (Case 1). Microscopic picture from pons.
(A) Necrotic zone is presented especially on the upper part as revealed by loose neuropil to be infiltrated by mononuclear and foamy cells. Many intact neurons are scattered. H & E, x 50.
(B) More advanced necrosis and vascular proliferation are shown. Note few intact neurons lying in necrotic zone and status spongiosus of neuropil particularly in lower half of the photomicrograph. H & E, x 100.

Figure 5. (Case 1). Microscopic pictures from cervical segment of spinal cord.
(A) Spongy degeneration, vascular proliferation and intact anterior horn cells are demonstrated. The area between arrowheads is further shown in B. H & E, x 50.
(B) Small blood vessels and infiltration of foamy macrophages are seen in loose necrotic zone. Intact neurons lie in necrotic area and at the edge. H & E, x 100.
Figure 6. (Case 2). Brain in Leigh’s disease. Scale is in centimeter.
(A) Mesencephalon exhibits gray-white necrotic areas (arrowheads), especially beneath the cerebral aqueduct (upper arrowhead).
(B) Pons and cerebellum demonstrates symmetrical necrotic zones (arrowheads) in each.
(C) Medulla shows necrotic foci (arrowheads).

Figure 7. (Case 2). Whitish necrotic areas (arrowheads) are scattered in the upper cervical segment of the spinal cord. Scale is in centimeter.
These necrotic zones tended to be symmetrical, especially in the dorsum of pons. They were 0.5 to 2.0 cm across, soft, dull, and friable. The right mammillary body was grossly intact. The optic nerves were not available for study. They were presumably attached to the left half of the brain that was taken away by the neurologist.

Microscopically, various necrotic foci contained numerous small blood vessels which were well outlined in Gomori’s stain for reticulin fibers (Fig. 8). Some blood vessels showed endothelial proliferation and infiltration of the walls by lymphocytes, plasma cells, and histiocytes (Fig. 9). Numerous lipid-laden macrophages (Fig. 10) and microglia were also observed in the necrotic region, along with gliosis (Fig. 11). Neurons, however, were relatively intact in these zones of necrosis (Fig. 12). Focal chronic nonspecific meningitis was also detected (Fig. 13). The pathologic changes of the cervical segment of the spinal cord were strikingly similar to those seen in the brain. Foci of necrosis with neovascularization, gliosis, and relatively intact anterior horn cells were observed (Fig. 14).

Figure 8. (Case 2). Histopathologic features.
(A) Necrotic focus contains numerous reactive cells and small blood vessels. H & E, x 50.
(B) Plentiful blood vessels are well outlined in Gomori’s silver impregnation x 50.
Figure 9. (Case 2). Vascular changes.
(A) Endothelial hyperplasia is shown. H & E, x 100.
(B) Vasculitis is depicted. H & E, x 50.
(C) A part of the same blood vessel in B shows numerous cellular infiltrates mainly lymphocytes. H & E, x 100.

Figure 10. (Case 2). Necrotic foci.
(A) Numerous foamy histiocytes are concentrated in an area of necrosis. H & E, x 400.
(B) Dark perikaryon of the histiocytes in necrotic zone is related to lipid content. Frozen section with oil-red-O stain, x 400.
Figure 11. (Case 2). Gliosis within lesion.

(A) Astrocytes with delicate processes are numerous in a lesion. Many of them are attached to the vascular walls by processes. H & E, x 50.

(B) Higher magnification of the area in the right upper corner in A shows astrocytes with delicate processes in relation to the vascular wall. H & E, x 100.

(C) A few plump astrocytes are demonstrated in a necrotic area; one of them has two vesicular nuclei. H & E, x 100.

(D) A bizarre astrocyte with homogeneous and glassy cytoplasm and eccentric vesicular nucleus lies in a necrotic zone. H & E, x 100.
Figure 12. (Case 2). Neurons within lesion.
(A) Many relatively intact neurons are disseminated within a necrotic zone as are plentiful mononuclear cells which are smaller than neurons. Also note vasculitis. This photomicrograph is taken from a locus celereus. H & E, x 50.
(B) A necrotic focus shows a relatively intact neuron, a cluster of blood vessels, and scattered lymphocytes and microglia. H & E, x 400.
(C) and (D) Two neurons with nuclei having distinct nucleoli creating fish-eye appearance lie within the liquefied neuropil, x 400 each.

Figure 13. (Case 2). Nonspecific inflammatory changes.
(A) The leptomeninges over cerebellar folium is infiltrated by many reactive cells. Layer of granular neurons is seen below. H & E, x 50.
(B) Higher magnification of the same lesion in A shows many lymphocytes, histiocytes, rod-shaped microglia, and few plasma cells representing nonspecific meningitis H & E, x 100.
The pathological diagnosis was subacute necrotizing meningo-encephalomyelopathy (Leigh’s disease) in an adult woman.

**Discussion**

Typical pathologic features of Leigh’s disease consist grossly of necrotic lesions which can be seen with the unaided eye in the mesencephalon and brainstem. They appear as gray, soft, friable, and slightly sunken zones which are often, but not always, symmetrical.\(^{2-18}\) The tegmentum of the midbrain and pons, periaqueductal gray matter, and posterior colliculi are often affected. Medullary lesions may affect the floor of the fourth ventricle and the inferior olivary nuclei. The lesions, moreover, may be located in the basal ganglia, especially putamen and substantia nigra. They are less common in the thalamus, centrum semiovale, and optic pathways. Sparing of the mammillary bodies is typical. Concerning the cerebellum, the lesion is common in the dentate nuclei and white matter, but is less frequent in the cortex and peduncles. The spinal cord may be affected. Involvement of the peripheral nerves is inconsistent.

Microscopically, severe sponginess of neuropil, necrosis, and infiltration of such cells as lymphocytes, polymorphonuclear cells, histiocytes, plasmacytes, and microglia are often seen as are glioses. Lipid-laden histiocytes are numerous in active lesions but are infrequent in less active or old lesions. Prominent proliferation of small blood vessels with endothelial hyperplasia is the most characteristic feature of Leigh’s disease, as is relatively intact neurons even in the necrotic area.\(^{2-18}\) Such gross and microscopic features were present in the brain and spinal cord of our two patients. Hence, we are certain about our pathologic diagnosis of subacute necrotizing encephalomyelopathy. Although the optic nerves were not studied pathologically, it is not essential that they must be examined in rendering the pathologic diagnosis of Leigh’s disease. When variously described pathologic features are detected in any part of the CNS, the pathologic diagnosis of Leigh’s disease can be made. The diagnosis, thus, can be rendered by biopsy of lesions such as from the brainstem.\(^{13}\)

Although the pathologic features in our two patients are quite similar to those of Wernicke’s encephalopathy we do not consider our cases to represent Wernicke’s encephalopathy. Both patients were not alcoholic and the mammillary bodies were intact. Thus we exclude from our review cases of Leigh’s disease described as associated with chronic alcoholism and with involvement of the mammillary bodies.\(^{19-21}\)

Although confusion between multiple sclerosis and Leigh’s disease has occurred clinically\(^{4,11}\) the two conditions can be distinguished pathologically. Multiple sclerosis is chiefly the disease of white matter; most lesions are scattered in the latter. Lesions of Leigh’s disease involve both gray and white matter, especially
Table 1. Summary on 15 cases of subacute necrotizing encephalomyelopathy (Leigh’s disease) in adults.

<table>
<thead>
<tr>
<th>No</th>
<th>Author(s) &amp; year of report</th>
<th>Age (yrs) at onset</th>
<th>Sex</th>
<th>Neurologic manifestations</th>
<th>Topography of CNS lesions</th>
<th>Histopathology</th>
<th>CT</th>
<th>MRI</th>
<th>General autopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Solheid et al, 1971(2)</td>
<td>21 23</td>
<td>M</td>
<td>Psychomotor retardation &amp; focal seiurces. Terminal L focal seiurces, L hemiparesis, nystagmus, relapsing stupor &amp; coma</td>
<td>Putamen, subthalamic nucleus, substantia nigra, brainstem, L cerebellum &amp; spinal cord</td>
<td>Necrosis, capillary proliferation, demyelination in brainstem &amp; spinal cord</td>
<td>ND</td>
<td>ND</td>
<td>Angioma of cerebellum</td>
</tr>
<tr>
<td>2</td>
<td>Martin, 1972(3)</td>
<td>43 43</td>
<td>M</td>
<td>Depression, loss of appetite &amp; malaise. Terminal R hemiparesis &amp; generalized seiurces</td>
<td>Cortex, optic chiasm, putamen, hypothalamus, subthalamic nucleus &amp; brainstem</td>
<td>Necrosis, capillary proliferation &amp; neuronal preservation</td>
<td>ND</td>
<td>ND</td>
<td>Insignificant</td>
</tr>
<tr>
<td>3</td>
<td>Ulrich &amp; Fankhauser Mauri, 1978(4)</td>
<td>31 31 4/12</td>
<td>M</td>
<td>Visual impairment, palsy of CN VI, ptosis &amp; tremor of hands</td>
<td>Midbrain &amp; brainstem</td>
<td>Necrosis, capillary proliferation &amp; neuronal preservation</td>
<td>ND</td>
<td>ND</td>
<td>Tracheobronchitis, pulmonary hemorrhage &amp; cardiac dilatation</td>
</tr>
<tr>
<td>4</td>
<td>Ho et al, 1979(5)</td>
<td>54 54</td>
<td>F</td>
<td>Sudden onset of saddle paresthesias &amp; incontinence of urinary bladder. Terminal paraparesis, flaccidity of legs, absence of reflexes &amp; lose of all sensations below T10</td>
<td>Midbrain, upper pons, periadequate gray matter, floor of fourth ventricle, medulla oblongata &amp; spinal cord.</td>
<td>Loosening of ground substance, gliosis, necrosis, proliferation of microglia, formation of microcysts, proliferation of small blood vessels &amp; endothelial cells &amp; preserved neurons</td>
<td>ND</td>
<td>ND</td>
<td>Confluent broncho-pneumonia</td>
</tr>
<tr>
<td>5</td>
<td>Kalimo et al, 1979(6)</td>
<td>22 23</td>
<td>F</td>
<td>Bilateral optic atrophy, hyperactive tendon reflexes, L plantar extensor response, paresthesia of L upper limb, ataxia, L hemiparesis, depression, paranoid, dementia &amp; R hemiplegia</td>
<td>Old necrosis of head of R caudate nucleus &amp; R occipital lobe. Optic atrophy</td>
<td>Hemorrhagic necrosis, spongy neuropil, proliferation of capillaries, gliosis &amp; preserved neurons</td>
<td>ND</td>
<td>ND</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Ho et al, 1982(7)</td>
<td>34 34</td>
<td>F</td>
<td>Blurred vision, malaise, sudden unconsciousness &amp; associated with Addison’s disease, Hashimoto’s disease &amp; diabetes mellitus</td>
<td>Well demarcated, gray &amp; dusky symmetrical lesions in tegumentum of midbrain &amp; pons, floor of fourth ventricle, optic chiasm &amp; cervical segment of spinal cord</td>
<td>Proliferation of small blood vessels with occasional perivascular lymphocytic infiltration, astrocytosis, proliferation of microglia &amp; preserved neurons</td>
<td>Normal</td>
<td>ND</td>
<td>Idiopathic adrenitis fibrosis of &amp; thyroid gland</td>
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<tr>
<td>No</td>
<td>Author(s) &amp; year of report</td>
<td>Age (yrs) at onset</td>
<td>Sex</td>
<td>Neurologic manifestations</td>
<td>Topography of CNS lesions</td>
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<tr>
<td>7</td>
<td>Hegedüs &amp; Nemeth, 1984&lt;sup&gt;44&lt;/sup&gt;</td>
<td>49 49</td>
<td>M</td>
<td>L progressive hemiparesis, instable gait, ataxia, frequent loss of consciousness, mild bilateral papilledema, exaggerated tendon reflexes, L pyramidal tract signs, lethargic disorientation, confusion &amp;akinetic mutism</td>
<td>Brainstem, periaqueductal gray matter, L inferior colliculus, L cerebellar hemisphere, thalamic nuclei, subthalamic bodies, R pallidum, L superior frontal gyrus, hydrocephalus due to narrowing of cerebral aqueduct</td>
<td>Severe proliferation of small blood vessels, foamy cells, necrosis, astrocytosis, proliferation of microglia, marked narrowing of cerebral aqueduct &amp; demyelination of optic nerves and tracts</td>
<td>ND</td>
<td>ND</td>
<td>Ureteritis, thrombosis of R iliac vein, massive pulmonary embolism</td>
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<tr>
<td>8</td>
<td>Gray et al, 1984&lt;sup&gt;4&lt;/sup&gt;</td>
<td>21 31</td>
<td>F</td>
<td>Visual impairment, ptosis, bilateral CN VI palsy, R facial palsy &amp; R extensor plantar response, Terminal drowsy, chewing movement, pinpoint &amp; nonreactive pupils, bilateral facial palsy, bilateral extensor plantar response, hyperthermia, respiratory failure &amp; death</td>
<td>Bilateral necrosis of head of caudate nuclei, thalami, internal capsules &amp; walls of third ventricle. Old lesions in posterior parts of cerebral peduncles, atrophy of optic chiasms &amp; preserved mammillary bodies</td>
<td>Two types of lesions namely chronic changes of optic chiasm &amp; cerebral peduncles characterized by myelin loss, status spongiosus, astrocytosis, marked proliferation of capillaries &amp; endothelia hyperplasia; Recent changes characterized by necrosis of neuropil with edema, lipid-laden macrophages, lymphocytic cuffing of blood vessels, capillary proliferation &amp; preserved neurons</td>
<td>ND</td>
<td>ND</td>
<td>Area of low density of thalami, anterior limbs of internal capsules &amp; spleenium of corpus callosum</td>
</tr>
<tr>
<td>9</td>
<td>Maso et al, 1984&lt;sup&gt;10&lt;/sup&gt;</td>
<td>57 57</td>
<td>M</td>
<td>Slurred speech, ataxia, nystagmus, extrapyramidal rigidity, decreased tendon reflexes, bilateral optic atrophy &amp; clonic jerks</td>
<td>Softening of striated nuclei, pons &amp; medulla oblongata. Focal cerebellar atrophy. Preserved mammillary bodies</td>
<td>Cavitory necrosis, moderate capillary proliferation &amp; neuronal preservation. Patchy demyelination of optic nerves &amp; tracts. Severe gliosis, cerebellar atrophy &amp; demyelination of dentate region</td>
<td>Normal at beginning. Slow enlargement of fourth ventricle at later period</td>
<td>ND</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>No</td>
<td>Author(s) &amp; year of report</td>
<td>Age (yrs) at onset at death</td>
<td>Sex</td>
<td>Neurologic manifestations</td>
<td>Topography of CNS lesions</td>
<td>Histopathology</td>
<td>CT</td>
<td>MRI</td>
<td>General autopsy findings</td>
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<td>10</td>
<td>Kissel et al, 1987(15)</td>
<td>21</td>
<td>F</td>
<td>Difficulty in balancing body, gait disturbance, intermittent diplopia, speech disturbance, urinary incontinence, decreased alertness, impaired extraocular movements, nystagmus, impaired upper gaze &amp; general motor weakness</td>
<td>Cavitary lesions of thalami, basal ganglia, midbrain, periaqueductal gray matter, floor of fourth ventricle, substantia nigra &amp; mild atrophy of optic nerves</td>
<td>Cavitation in basal ganglia bridged by blood vessels, gliosis, neuronal depletion but preservation of neurons &amp; midbrain tegmentum</td>
<td>Normal</td>
<td>Focal area of increased signal intensity in region of periaqueductal gray matter &amp; midbrain tegmentum</td>
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<tr>
<td>11</td>
<td>Cummiskey et al, 1987(16)</td>
<td>34</td>
<td>F</td>
<td>Automatic respiratory failure, limited upward gaze, bilateral facial weakness &amp; decreased gag reflex</td>
<td>Diencephalon, periaqueductal gray matter in pons, floor of fourth ventricle (medulla) &amp; cervical segment of spinal cord</td>
<td>Not described but gave diagnosis of subacute necrotizing encephalomyelopathy</td>
<td>ND</td>
<td>—</td>
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<td>12</td>
<td>Sahni et al, 1987(17)</td>
<td>36</td>
<td>F</td>
<td>Not described</td>
<td>Medulla oblongata</td>
<td>Staus spongiosus &amp; astrocytosis seen in CT-guided stereotactic biopsy</td>
<td>Contrast enhancing lesion of posterior medulla</td>
<td>Low intensity</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>Reynaud et al, 1988(18)</td>
<td>35</td>
<td>M</td>
<td>Behavioral changes, epileptic fits, ataxia, autonomic disorders, abnormal alimentary behavior &amp; dementia</td>
<td>Caudate nuclei, R putamen &amp; pallidum</td>
<td>Necrosis, hyperplasia of capillaries, severe status spongiosus &amp; preserved neurons.</td>
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<tr>
<td>No</td>
<td>Author(s) &amp; year of report</td>
<td>Age (yrs) at onset at death</td>
<td>Sex</td>
<td>Neurologic manifestations</td>
<td>Topography of CNS lesions</td>
<td>Histopathology</td>
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<td>General autopsy findings</td>
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<tr>
<td>14</td>
<td>Shuangshoti et al, current case 1</td>
<td>22 32</td>
<td>F</td>
<td>Bilaterally blurred vision, weakness of all limbs, numbness of hands &amp; feet</td>
<td>Thalami, R temporal lobe, R cerebral peduncle, substantia nigra, pons, medulla oblongata &amp; cervical segment of spinal cord</td>
<td>Necrosis, proliferation of small blood vessels &amp; endothelium, gliosis &amp; preserved neurons</td>
<td>Low density lesion in R thalamus, Homogeneous &amp; dense intramedullary lesion of cervical segment of spinal cord</td>
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<tr>
<td>15</td>
<td>Shuangshoti et al, current case 2</td>
<td>38 40</td>
<td>F</td>
<td>Paraparesis of lower limbs, difficulty in urination, optic neuritis, dysphagia, hyperesthesia &amp; formication of skin, blurred vision in R eye, bilateral extensor plantar responses, stupor &amp; coma</td>
<td>Thalamus, basal ganglion, centrum semiovale, mesencephalon, pons, medulla oblongata &amp; cervical segment of spinal cord</td>
<td>Necrosis, microglial proliferation, vascular proliferation &amp; endothelial hyperplasia, astrocytosis &amp; preserved neurons</td>
<td>—</td>
<td>—</td>
<td>Tracheobronchitis &amp; decubiti</td>
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</table>

CNS = Central Nervous System, CN = Cranial Nerve, R = Right, L = Left, M = Male, F = Female, CT = Computerized Tomogram, MRI = Magnetic Resonance Imaging, ND = Not Done.
the midbrain and brainstem around or near the cerebral aqueduct. To our knowledge, vascular changes as we have described previously and in the current study which were characterized by an increase in the number of blood vessels and proliferation of endothelial cells\(^{(18)}\) have not yet been observed in multiple sclerosis.

The clinical confusion between multiple sclerosis and Leigh's disease is probably related to the fact that both diseases have lesions disseminated in various parts of the CNS. Similar clinical manifestations, then, develop when some of these lesions are distributed in the same or similar region of the CNS although they are morphologically different.

To the best of our knowledge, only 15 adult forms of subacute necrotizing encephalomyelopathy have been recorded\(^{(2,14)}\) including our two cases presented here (Table 1). Some examples having initial symptoms in childhood which should be recognized as a juvenile form of Leigh's disease who survived to adulthood are excluded\(^{(22-24)}\).

Briefly, lesions of Leigh's disease in adults are frequently multiple. Basal ganglia, thalamus, brainstem, optic nerves, and spinal cord are often affected. Motor weakness and visual impairment are common, followed by ataxia, seizures, psychiatric disturbances, sensory manifestations, palsy of cranial nerves, and sleep disturbances. Most patients have been subacute with periods of remission and exacerbation in their clinical course as noted in our patients. The clinical diagnosis, thus, should be considered when patients develop an acute or subacute neurological manifestation beginning with visual impairment followed by brainstem dysfunction.

Only a few adult patients with Leigh's disease have been studied using CT brain scans. For instance, Whetsell and Plaitakis\(^{(22)}\) reported edema of the midbrain in one of their three patients. Gray et al\(^{(9)}\) described bilateral hypodensities in both thalami and anterior limb of the internal capsule. Mase et al\(^{(10)}\) noted enlarged fourth ventricle and cerebellar atrophy. Low density lesions in the right thalamus was also observed in our case 1. Delgado et al\(^{(24)}\) showed low density lesions of the striatum bilaterally in their questionable case of Leigh's disease. Kissel et al\(^{(11)}\) and Davis et al\(^{(26)}\) have studied subacute necrotizing encephalomyelopathy using magnetic resonance imaging (MRI). Symmetrical involvement of lesions had been noted in the basal ganglia, midbrain, and around the cerebral aqueduct with sparing of the mammillary bodies. These lesions showed increased signal intensity.

The cause of subacute necrotizing encephalomyelopathy is unclear but believed to be a metabolic disease associated with various defects in oxidative phosphorylation or mitochondrial DNA mutations.\(^{(14,27)}\) Kepes\(^{(24)}\) observed oncocytic transformation of the choroid plexus epithelium of a patient who died with Leigh's disease. Electron-microscopically he noted numerous abnormal mitochondria within the choroidal epithelial cytoplasm. There is no specific treatment for subacute necrotizing encephalomyelopathy. The patient invariably succumbs to the disease.

References


17. Montpetit JA, Anderson M, Carpenter S, Fawcett JS, Zborowska-Sluis D, Giberson HR. Subacute necrotizing encephalomyelopathy (a review and a study of two families). Brain 1971 Jan;94(1)1-30


