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A 35-year-old female with growth and developmental retardation, progressive ataxia, dementia and visual loss

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CLINICAL HISTORY

This female patient was born to healthy parents who were first cousins. Her elder brother and two paternal uncles had a disorder similar to hers. She began to walk at the age of 1 years and 6 months. During childhood, she was physically small and mentally retarded. To receive special education, she went to school on foot. Gait ataxia appeared at the age of 19 years, and gradually worsened thereafter. When she was 31 years of age, she became unable to walk unsupported. She showed progressive loss of vision and hearing, spoke fewer words than previously, and complained of fear and insomnia. At the age of 32 years, she was institutionalized at a facility for the severely handicapped. On admission, she showed dwarfism (113 cm in height), emaciation (18 kg in weight) and pigmentation of the skin. Her head was small and her face showed a senile-like appearance with sunken eyes, cataract and malpositioned teeth. Neurological examination disclosed severe impairment of hearing and vision, dysarthria, muscle hypertonia, truncal and limb ataxia, spontaneous extension of the toes, and emotional instability. Her mental age was between 1 and 3 years. Laboratory examination showed hyperuricemia and slow conduction velocity of the peripheral nerves. Ultrasonography of the abdomen demonstrated thinning of the renal cortex. Computed tomography of her head showed diffuse cerebral atrophy, ventriculomegaly, and symmetrical calcification of the basal ganglia and cerebellar medulla (Fig. 1). On magnetic resonance imaging, the calcified lesions showed T1- and T2-shortening. The cerebral white matter was atrophic and showed patchy T1- and T2- elongation (Fig. 1). At the age of 34 years, restlessness and anxiety worsened. She refused to eat, had epileptic attacks, and underwent hydration and medication with neuroleptic, hypnotic and antiepileptic drugs. Several months later, she became somnolent and developed fever, vomiting and hypertension, followed by coma, muscle rigidity and abnormal respiration. A high serum level of creatine kinase suggested a diagnosis of neuroleptic malignant syndrome. After approximately a week, she died at the age of 35 years.

PATHOLOGICAL FINDINGS

The patient's brain was small and atrophic, weighing 810 g. The leptomeninx was thickened in the parasagittal areas. The surface arteries were sclerotic. The right parietal lobe and insula showed softening and hemorrhage. On sectioning of the brain, there was atrophy of the cerebrum, cerebellum and brainstem, with enlargement of the ventricular system. The cerebral white matter, except the corpus callosum, was atrophic, grayish and devoid of normal luster. The bilateral basal ganglia were sclerotic and calcified. The cerebellar dentate nuclei were small and grayish.

Histologically, arteries of the brain surface showed thickening and kinking (Fig. 2a). Thrombosis was noted in an insular branch of the right middle cerebral artery (Fig. 2b). In the parietal and insular cortex, there was a large, fresh, hemorrhagic infarct. The rest of the cerebral cortex remained mostly intact except layer IV of the striate cortex, which showed severe neuronal loss and calcification (Fig. 3). The cerebral white matter showed patchy loss of myelin sheaths and axons, without fibrillary gliosis (Fig. 4). A small number of spheroids were scattered. The cerebral basal ganglia (especially the putamen and the outer segment of globus pallidus) and adjacent cerebral white matter showed calcification of blood vessels (annular) and

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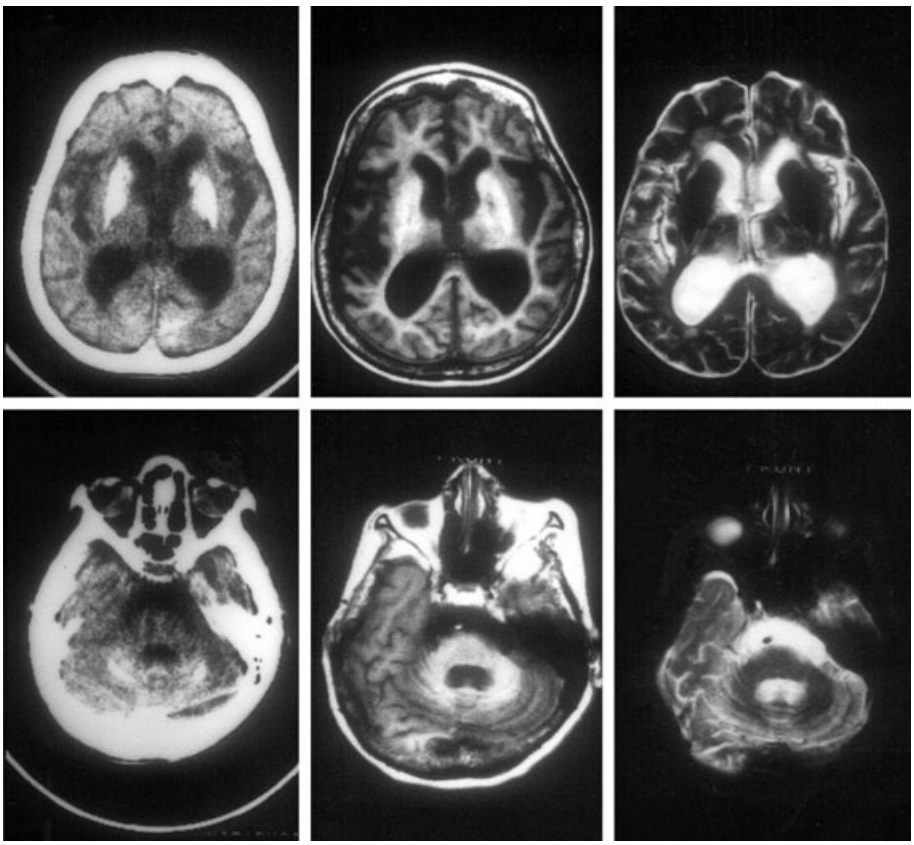

Fig. 1 Cranial computed tomography (left), T1-weighted (middle) and T2-weighted (right) magnetic resonance images, showing diffuse cerebral atrophy and calcification of the basal ganglia and cerebellum. The cerebral white matter showed volume loss, and contained patchy areas of T1- and T2-elongation.

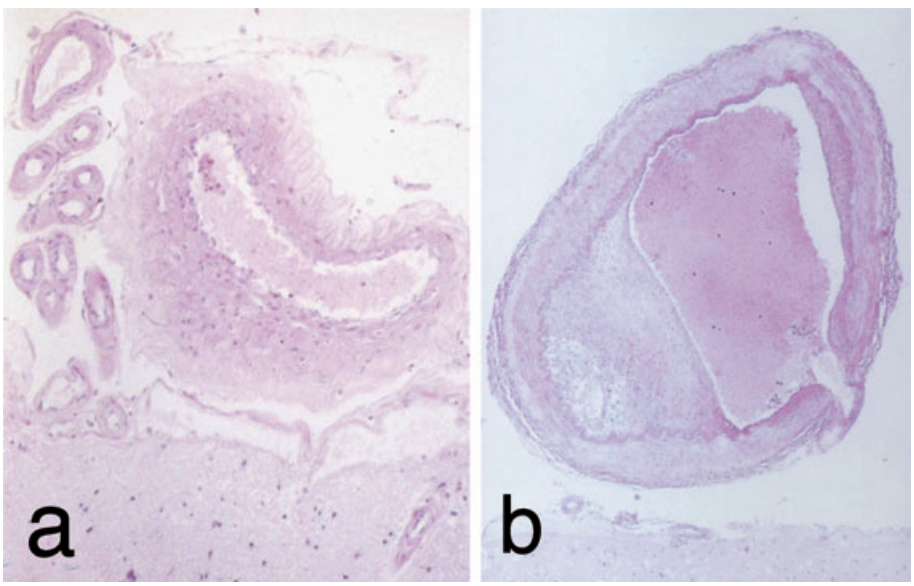

Fig. 2 Arteries of the brain surface showing thickening of the walls, kinking (a) and thrombosis (b) (HE staining).

parenchyma (dot-like) (Fig. 5), associated with a variable degree of neuronal loss. Astrogliosis was often noted in the perivascular areas (Fig. 5b). Binuclear astrocytes were occasionally seen. The cerebellar cortex showed atrophy of the molecular layer, loss of Purkinje and granular cells, and many torpedos (Fig. 6). Binuclear astrocytes were often noted in the subcortical region. The cerebellar medulla around the dentate nuclei showed calcification, loss of myelin sheaths and axons, astrogliosis, and occasional axonal swelling. In the substantia nigra, loss of neuromelanin, and many Marinesco bodies were noted. The reticular formation and fiber bundles of the brainstem, as well as

the white matter of the spinal cord, showed patchy loss of myelin. Axonal loss and spheroids were also noted in the posterior funicular nuclei. The inferior olivary nuclei showed moderate loss of neurons and hilar axons. Neurons of the spinal cord were reduced in number. Lipofuscin accumulation was noted in some of the remaining neurons. The spinal nerves (especially the anterior roots) showed segmental demyelination. In the skeletal muscles, there were small angular fibers and opaque fibers.

Systemic arteries, large and middle, showed marked atherosclerosis. In the kidneys, many glomeruli were atrophic with occasional crescent formation and hyalinization. Cardiac muscles showed lipofuscin accumulation. Nodular atrophy of the thyroid and acute bronchitis were also noted.

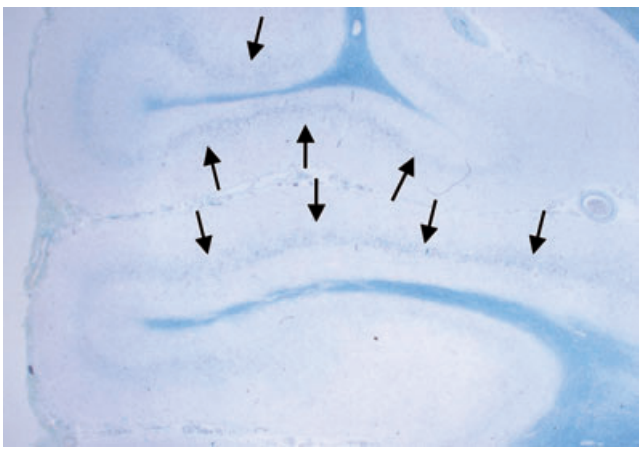

Fig. 3 Striate cortex. In the deep portion of the sulci, the Gennari's stria of layer IV was replaced with calcification (arrows) (Klüver-Barrera staining).

DIAGNOSIS

#1 Cockayne syndrome (CS), #2 Cerebral infarction.

DISCUSSION

Cockayne syndrome is a genetic disorder of DNA repair inherited as an autosomal recessive trait. The clinical diagnostic criteria of CS consist of findings such as cachectic dwarfism, mental retardation, microcephaly, cerebellar ataxia, retinal pigmentary degeneration, sensorineural deafness, progeria and intracerebral calcification. The present case had most of these features, and was diagnosed as having CS on a clinical basis. The onset of CS is usually in infancy or early childhood. The disorder is progressive, and patients usually die in their teens or twenties. In the present case, the onset was later, the course was slower, and the survival was longer than in most other CS cases.

Cytological studies of CS patients' cells have demonstrated impairment in the recovery of RNA synthesis after ultraviolet irradiation, which results from a defect in nucleotide excision repair (NER). There are two causative genes of CS, CSA and CSB. The protein products of these genes form a complex, initiating transcription-coupled repair (TCR), a subpathway of NER that rapidly removes DNA damage from the transcribed strand of active genes.[1]

The main neuropathological features of CS include micrencephaly, tigroid demyelination and intracerebral calcification, all of which were found in this patient's brain.

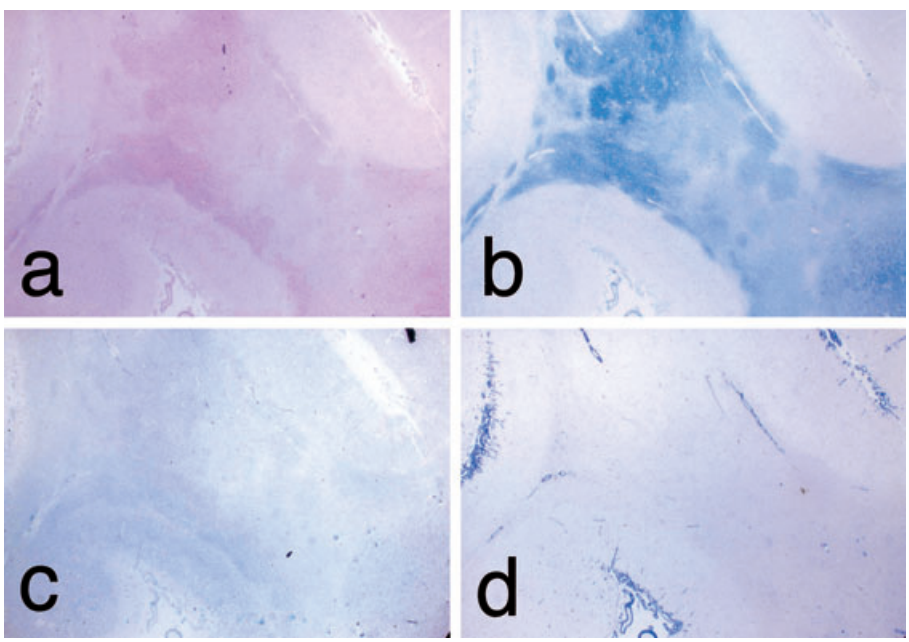

Fig. 4 Frontal lobe. The white matter showed patchy rarefaction (a, HE). Both myelin sheaths (b, Klüver-Barrera) and axons (c, Bodian) were reduced. Fibrillary gliosis was negligible (d, Holzer).

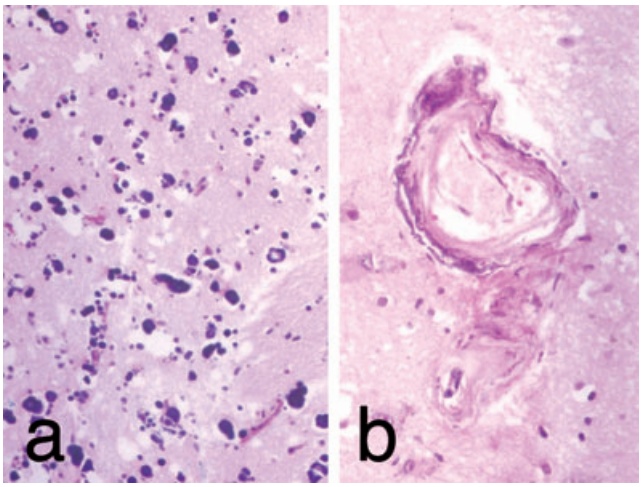

Fig. 5 Putamen. Dot-like calcification of the cerebral parenchyma (a) and ring-like calcification of the vascular walls (b). Astrogliosis was noted around the blood vessels (b) (HE staining).

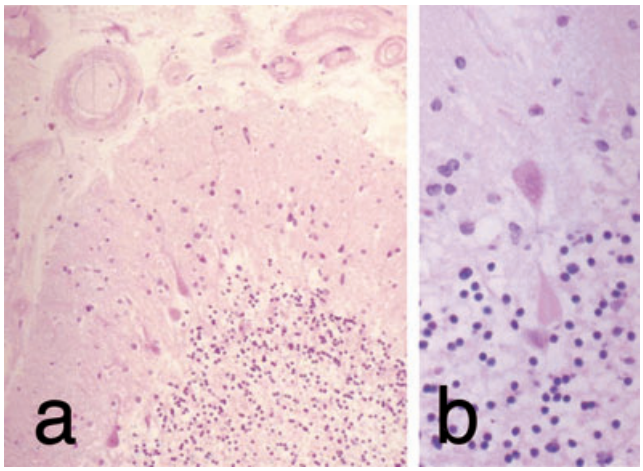

Fig. 6 Cerebellar cortex showing atrophy, loss of Purkinje and granular cells, kinking of the surface arteries (a), and torpedos (b) (HE staining).

Loss of myelin affects both the central and peripheral nervous system. In the brain of this case, axons were also reduced in number, to an extent comparable to that of myelin sheaths. It is unclear whether these findings represent a developmental disorder (dysmyelination) or a degenerative change (demyelination). The absence of fibrillary gliosis is suggestive of the former, whereas the presence of axonal spheroids is compatible with the latter.

In brains with CS, calcification most frequently occurs in the basal ganglia and cerebellum. In these brain regions, there are astrocytic changes, such as perivascular gliosis and binuclear astrocytes, which may implicate astrocytic dysfunction in the pathogenesis of the calcified lesions. Calcification also affects the cerebral cortex occasionally. In the present case, cortical calcification was confined to layer IV (Gennari's line) of the striate cortex. This unique distribution may partially account for the progressive loss of vision in this patient.

The brains of CS patients show findings of precocious aging. Various neuronal changes, such as neurofibrillary tangles, Hirano bodies and lipofuscin accumulation, have previously been described. However, these were unremarkable in the present case, with the exception of the many Marinesco bodies found in the substantia nigra. Instead, this case had severe vascular changes. Prominent arteriosclerosis of the cerebral arteries caused a large cerebral infarction at the terminal stage, in conjunction with the hemodynamic changes related to the neuroleptic malignant syndrome.

In brief, the neuropathology of CS indicates a mixture of developmental disorder, degeneration, and premature aging involving neurons, astrocytes, myelin sheaths and blood vessels. However, how this is produced by a defect in TCR remains to be solved. Recent studies have shown that TCR is important not only in the repair of DNA damage, but also in the recovery of inhibited transcription and in the regulation of transcriptional activity.[2] Defective TCR may lead to accumulation of DNA damage, possibly by reactive oxygen species,[3] which in turn causes degeneration and accelerates aging. However, aberrant regulation of transcription may account for the developmental disorder in CS brains.

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