Dentato-rubro-pallido-luysian atrophy: a clinico-pathological study

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SUMMARY Clinical and neuropathological descriptions are given of four cases of an uncommon disease, characterised by simultaneous degeneration of the dentato-rubral and pallido-luysian systems. These four are compared with sixteen previously described cases, and the group as a whole is compared and contrasted with other multisystem degenerations, such as olivo-ponto-cerebellar atrophy and Friedreich's ataxia. A pathological feature described here for the first time is degeneration of the fastigio-vestibular system. Clinically, there are three main types of the disease; (1) an ataxo-choreoathetoid type, (2) a pseudo-Huntington type, and (3) a myoclonic-epileptic type. There are familial cases of types 2 and 3. Oculomotor disturbances, associated with atrophy of the brainstem tegmentum, are observed in cases of types 1 and 3.

Dentato-rubro-pallido-luysian atrophy was described by Titica and van Bogaert in 1946.¹ Further cases were reported by Smith, Gonda and Malamud,² Verhaart³ and Neumann.⁴ Characteristics of these cases were coexisting ataxia and choreoathetosis with degenerative changes involving both dentato-rubral and pallido-luysian systems. During the last few years more cases have been reported, particularly in Japan; the condition, however, is still little known and its relationship with other degenerative diseases poorly understood. In this paper we describe four cases which came to necropsy, with their clinical and neuropathological features, and give a review of the literature of the subject.

Case reports

Case 1: ST. Age 27 yr, male

Family history: his mother had had speech and gait disturbances since her 18th year, and died at 33. No further details were available. Present illness: at the age of 15 years, the patient noticed slurred speech and twitching around the corner of his mouth. Six months later his movements became slower and his gait became unsteady. At 18 he had to give up his job as a barber because his

fingers were clumsy. After that bilateral ptosis and distal muscle atrophy developed. At the age of 23, athetoid movements and a peculiar abnormal posture appeared in his hands and legs. The patient progressively deteriorated and had to be admitted to hospital at age 26 years.

On admission: the patient was alert and had normal intelligence. Speech was ataxic and slow. He had lost control of head movements and was bedridden. Support was required to sit upright to eat. His face had a myopathic look, with drooping mouth and ptosis. External ocular movements showed several abnormalities, such as bilateral upward gaze palsy, poor conjugation, incomplete abduction of left eye and isotropic deviation on downward gaze. The pupils were normal in size and reflexes. Visual and auditory functions were normal, and ophthalmoscopic examination failed to show any abnormalities. Dysphagia was accompanied by mild tongue atrophy. Muscle atrophy was seen in all extremities, with fibrillary twitchings. Muscle tone was essentially hypotonic. Tendon reflexes were normal, with spontaneous Babinski and positive dorsal responses. There were no sphincter disturbances. Athetotic movements were present in the hands, fingers, and the right corner of the mouth, but there were no seizures or myoclonus. CSF and EEG showed no specific abnormalities. IQ was 86 (WAIS). The illness progressed; perphenazine, trihexyphenidyl, levodopa were all ineffective. The patient died of cachexia at age 27.

Neuropathology: macroscopically no gross abnormalities were noticed except a mild atrophy of the brainstem. The cerebral cortex and white matter were well preserved. The striatum showed no marked atrophy or discolorations, but seemed to have a minimal depopulation of large neurons. The pallidum, especially the lateral segment, was markedly shrunken. Neurons were almost completely lost (fig 1),

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Fig 1 Case 1, Putamen (P) shows no marked change. Globus pallidus (G) shows almost complete neuronal loss, with severe gliosis, and scattered pigment granules. Klüver-Barrera $\times 26$.

Fig 2 Case 1, (a) Dentate nucleus. Marked loss of neurons and severe gliosis. HE $\times 18$. (b) Remaining nerve cell showing so-called grumose degeneration. Bodian $\times 365$.

with severe gliosis; the remaining neurons were atrophic or vacuolated. Some of them appeared as "ghost" cells, with phagocytosis. Pigment granules were scattered over the affected region of the pallidum. These were brownish-yellow in the H and E stain, and greenish-blue in the Nissl stain. The glial reaction, which consisted mainly of protoplasmic astrocytes, was striking, but fibrous astrocytes were inconspicuous. The projection fibres from the pallidum, the lamina medullaris, the ansa lenticularis, and the lenticular fasciculus, showed atrophy, with marked demyelination and fibrous astrocytosis. In the subthalamic nucleus neuronal loss was accompanied by gliosis. The thalamus and the amygdala were intact. In the brainstem, the main pathological changes were located in the tegmentum. The midbrain tegmentum was wasted, whereas the peduncular portion appeared normal. The posterior commissure and the inferior colliculi were gliotic. The oculomotor nuclei showed lipofuscin deposits, but neither neuronal loss nor Alzheimer's neurofibrillary changes were seen. The medial longitudinal fasciculi, the medial lemnisci, and the central tegmental tracts were markedly demyelinated, and this change was detectable caudalward down to the medulla oblongata, with the most prominent damage occurring at pontine levels. The red nuclei showed moderate loss of small neurons, and the Holzer stain revealed marked gliosis in the red nuclei and in the superior cerebellar

Fig 3 Case 1, atrophy of the superior cerebellar peduncle and of the tegmentum, with gliosis. Gliosis of the medial longitudinal fasciculi, central tegmental tracts, juxtarestiform body and medial lemnisci. Holzer $\times 2.7$.

Fig 4 Case 1, Purkinje cells are well preserved. HE $\times 75$.

peduncles. The trochlear nuclei and the substantia nigra were well preserved. Despite the tegmental atrophy, the ventral portion of the pons was spared. The pontine nuclei, the transverse fibres, the pyramidal tracts, and the middle cerebellar peduncles were all intact. In the medulla, the inferior olivary nuclei showed severe gliosis, and the neurons appeared slightly atrophic and pycnotic, but were not decreased in number. Gliosis extended a short distance along the olivo-cerebellar bundles. The superior vestibular nuclei showed relatively severe degeneration, with milder changes in the inferior vestibular nuclei. The spinal cord showed slight demyelination in the spinocerebellar tracts and the posterior columns, especially in the columns of Goll. This was seen at all levels of the spinal cord, but was more obvious at higher levels. The cells of Clarke's column were mildly decreased in number. In the lower spinal cord, mild demyelination was seen in the pyramidal tracts, with anterior horn cell degeneration.

The cerebellum showed the most severe changes, particularly in the dentate nuclei and fastigial nuclei, where neurons were markedly decreased in number and replaced by glial cells (fig 2a). The remaining neurons were atrophic and pycnotic; some were vacuolated, and others swollen. The Bodian stain revealed clusters of degenerated terminal buttons at the sites of the missing neurons (so-called grumose degeneration) (fig 2b). The superior cerebellar peduncles were thin. The Holzer stain (fig 3) showed glial proliferation up to the level of the red nuclei. The two projection bundles from the fastigial nuclei to the vestibular nuclei were demyelinated, with dense gliosis. The Holzer stain clearly demonstrated the uncinate fasciculus running down into the roof of the fourth ventricle. In contrast to the severe degeneration of the dentate nuclei, Purkinje cells were fairly well preserved (fig 4). The granular layer and the white matter were not affected.

Case 2: MT. Age 28 yr, male

This man was adopted at age 5. No family or past history is available.

History of present illness: around the age of 13 years, his teacher observed some alteration of speech and of posture in running. The progress of the illness was so slow that he could work in a factory until he was 21, when his staggering gait and slurred speech interfered with his work. He was admitted to hospital at age 21. Status on admission: the

patient was alert and normal in intelligence. Speech was slow and slurred. He walked unsteadily on a wide base, and showed dyssynergia between hip and leg movements. The centre of gravity lay posteriorly, and he tended to fall backward when in a squatting posture. The Romberg sign was negative. The pupils were normal in size and reflexes. The extraocular movements had some limitation of convergence, and showed upward gaze palsy in reflex and voluntary movements. The tongue moved slowly, with dysphagia when drinking. The finger-to-nose test and the rapid alternating movement test elicited adiadochokinesia and athetoid movements. The heel-to-knee test showed hypermetria. Deep tendon reflexes were decreased in the upper extremities and increased in the lower ones, with ankle clonus. Muscle tone was flaccid in the arms, spastic in the legs. The plantar reflex was flexor. Pain, tactile, and vibratory senses were slightly diminished in the distal parts of the limbs. There were no generalised seizures.

During hospitalisation, the signs and symptoms increased in severity. Adiadochokinesia, hypotonia, and hypermetria became gradually less prominent, but persisted until age 24. After that time, rigidity set in, and athetotic movements finally became conspicuous at age 25. Pyramidal signs, such as hyper-reflexia and Hoffmann's sign, appeared for a while. An initial nystagmus changed to tremulous movement: later an abducted eye showed monocular nystagmus. Voluntary eye movements were also impaired in both vertical and horizontal directions. He fell backward more easily, but could slide along on his buttocks until age 26. There were no seizures or myoclonus. Later he became completely bedridden, with severe emaciation. He died at age 28.

Laboratory data: the CT scan and pneumoencephalogram showed tegmental atrophy of the brainstem and dilatation of the fourth ventricle. The electro-ophthalmogram

Fig 5 Case 2, midbrain, gliosis of the red nuclei and of the medial longitudinal fasciculi. Holzer $\times 5$.

Fig 6 Case 2, cervical segment of the spinal cord. Partial demyelination of the spino-cerebellar tracts and gracile fasciculi. Klüber-Barrera $\times 5$.

revealed multiple abnormalities such as nystagmus and vertical and horizontal saccadic pursuits. Optokinetic nystagmus was suppressed horizontally and lost vertically. The CSF and EMG were normal.

Neuropathology: The cerebral cortex and white matter were normal. The striatum and thalamus showed no abnormalities. The lateral segment of the pallidum showed mild neuronal loss and scattered pigment deposits, without gliosis. In the projection fibres from the pallidum, faint demyelination and gliosis were present, but no marked changes were seen in the subthalamic nucleus except for slight gliosis. The optic nerve and the lateral geniculate body showed mild gliosis. In the midbrain, the tegmental portion was atrophic. The medial longitudinal fasciculi, the medial lemnisci and the central tegmental tracts were moderately demyelinated, with gliosis (fig 5), down to the lower level of the medulla. The red nucleus showed mild rarefaction of the small neurons, but the oculomotor nuclei and the substantia nigra were not involved. In contrast to the tegmental atrophy, the basilar portion of the pons was normal in size. The pontine nuclei, the transverse bundles and middle cerebellar peduncles were all intact. In the medulla oblongata, there was moderate degeneration of the vestibular nuclei, relatively milder in the inferior vestibular nuclei. The inferior olivary nuclei and the nuclei of the lower cranial nerves were all intact. In the spinal cord, the posterior spinocerebellar tracts were slightly demyelinated (fig 6); Clarke's column cells, the lateral funiculi, and anterior horn cells were not affected. The cerebellum showed the most prominent changes in this case. The dentate nucleus showed complete neuronal loss, and had a spongy appearance because of multiple empty holes where neurons had been. Grumose degeneration and dense gliosis were present. The superior cerebellar peduncles were atrophic, and showed severe axonal degeneration with marked gliosis, which was seen up to midbrain level. Degeneration of the fastigial nuclei was also diffuse and severe. Both the uncinate fasciculi and the juxtarestiform bodies showed demyelination and gliosis. At pontine level, the juxtarestiform bodies, which run down between the inferior cerebellar peduncles and the lateral vestibular nuclei, appeared as well-demarcated lesions in the Holzer stain. The emboliform and globose nuclei were also affected, but more mildly than the fastigial nuclei. The

cerebellar cortex and white matter were well preserved.

Case 3: KO. Age 48 yr, male

Family history: A sister had a similar illness, which was clinically diagnosed as Huntington's chorea. Another sister and her four children had seizures (reported by Takahata *et al.*⁵ Family F). Around the age of 35 years, the patient staggered occasionally. After age 41 his legs began to move spontaneously after drinking alcohol or under mental stress. At the same time personality changes and memory disturbances were noticed. At age 48, Huntington's chorea was suspected, and he was admitted to hospital.

On admission, the patient was irritable and emotionally labile, and had a low IQ (verbal 84, performance 72 by WAIS). His speech was slurred and explosive. He walked unsteadily, and was unable to walk on his heels or on tip-toe. Pupils and external ocular movements were not affected, and there was no nystagmus. Other cranial nerves were intact. Slight hypermetria was observed in the heel-to-knee test, but not in the finger-to-nose test. Rapid alternating movements were awkward. Choreic movements occurred in the fingers and around the mouth, but scarcely on the trunk or in the proximal parts of the extremities. Choreic movement was provoked by emotional stress and by voluntary movement. Deep tendon reflexes were normal, and the plantar responses were flexor. No muscle atrophy was seen, but muscle tone was slightly hypotonic at the wrist joints. There were no sensory or sphincter disturbances. CSF and EEG were normal.

Hospital course: In this case, choreic movement was the most prominent feature throughout the clinical course, whereas cerebellar and spinal cord signs were minimal even in the early stage. The abnormal movements, especially those in the upper limbs, were hard to classify as either ataxic or choreic. In the lower extremities, the movements appeared closer to ataxia. The illness took a progressive course, with gradual deterioration of motor function and mental state. At the age of 52, his gait became broad-based and he tended to fall backward. Tendon

Fig 7 Case 3, dentate nucleus. Loss of nerve cells, with spongy appearance. Marked gliosis. Klüber-Barrera $\times 100$.

reflexes became hyperactive and muscle tone decreased. Intelligence regressed (IQ verbal 64, performance 60) and his negative behaviour annoyed the medical staff. He refused assistance, even in feeding, and finally died of cachexia at the age of 54 years.

Neuropathology: The cerebral hemispheres appeared slightly shrunken. There was mild gliosis in the cortex, and slight diffuse demyelination in the white matter. The pallidum showed severe degeneration, particularly in the lateral segment. Neuronal loss was severe, with protoplasmic astrocyte proliferation. There was much lipofuscin deposition in the degenerated neurons, and massive pseudocalcification and corpora amylacea around the blood vessels in the pallidum. Except for mild gliosis, the subthalamic nucleus showed no marked abnormalities. The striato-nigral system and the thalamus were intact. In the midbrain, the red nucleus showed marked gliosis without nerve cell loss. Tegmental atrophy of the brainstem was present but less prominent than in the other cases. The medial longitudinal fasciculi, the central tegmental tracts, and the medial lemnisci were not involved. The oculomotor and trochlear nuclei were intact. In the pons, the pontine nuclei, the transverse fibres and the middle cerebellar peduncles were not affected. In the medulla the vestibular nuclei were mildly degenerated but the inferior olivary nuclei were not involved. At the lowest level of the medulla, moderate demyelination was seen in the posterior columns, particularly in the columns of Goll, and in the spinocerebellar tracts, matching the lesions of the spinal cord found in the other cases. The spinal cord could not be examined. In the cerebellum, the dentate nuclei were most severely affected. Almost all the neurons were lost, leaving empty holes (fig 7). In the remaining cells there were atrophic and vacuolar changes and grumose degeneration, with dense gliosis. Serial sections disclosed that these lesions were most severe in the medial parts of the nucleus surrounding the hilum. The superior cerebellar peduncles showed loss of axons. The Holzer stain showed severe gliosis from the hilum of the dentate nucleus to the highest level of the fourth ventricle. The other deep cerebellar nuclei, especially the fastigial nuclei, showed severe degeneration, associated with demyelination of the uncinate fas-

Fig 8 Case 4, gliosis of thalamus (T) and globus pallidus (G). Holzer $\times 4$.

Fig 9 Case 4, subthalamic nucleus. Marked gliosis. HE $\times 14$.

ciculi and juxtarestiform bodies. The Purkinjé cells and the granular layer were not affected.

Case 4: YS. Age 38 yr, male

Family history: The patient's mother was said to fall frequently, and had died at 33 years. No further history was available. The patient had noticed staggering gait, slurred speech and pins-and-needles in the lower extremities since age 21 years. In the initial 4–5 years of his illness, intermittent dizziness, tinnitus, nausea, and vomiting occurred. The pins-and-needles sensations spread to all four extremities in a few years. At the age of 23 years, he complained of difficulty in reading and of double vision on lateral gaze. The unsteadiness of his gait increased, and difficulty in swallowing developed. He was hospitalised at the age of 24.

The whole duration of illness was 13 years and 7 months. The overall course was slowly progressive. From 24 to 26 years old, it fluctuated, and included an almost asymptomatic period of one year. On admission, the relatively constant and prominent clinical features were ataxia and paraesthesiae of distal parts of the extremities. There were athetotic movements of the tongue and fingers, but these were less striking. Other signs and symptoms, such as horizontal nystagmus, upward gaze palsy and dysphagia fluctuated, with remissions and exacerbations, until the age of 28, and then became continuous and progressive. Pyramidal signs, such as increased tendon reflexes and positive Babinski sign, and disturbances of hearing and taste, appeared transiently. After the age of 30, athetotic movements developed in the face and in all four limbs. As muscle atrophy progressed, the patient became completely bedridden, and lost the ability to control his head and to keep his eyes open. Eye movements were limited, not only in the vertical but also in the horizontal direction. His speech was severely affected, but he remained alert. There were no seizures or myoclonus throughout his clinical course. At the age of 38 he died of aspiration pneumonia, with the clinical diagnosis of multiple sclerosis.

Neuropathology: The pathological changes were identical in nature, but more severe than in any of the other cases. There were intense glial reactions, with proliferation of

protoplasmic astrocytes and active microglia, in all the affected basal ganglia and thalamus, which were not observed in the other cases (fig 8). The optic nerves and the lateral geniculate bodies also showed moderate glial reactions, but the cerebral cortex and white matter were not affected. The pallidum was the most severely affected region, particularly the lateral segment, neuronal loss being almost complete. The subthalamic nucleus showed severe neuronal loss with gliosis (fig 9); thalamic nuclei were also affected by diffuse gliosis, but without obvious neuronal depopulation. Tegmental atrophy from the mid-brain to the pons was severe, and most marked at mid-pontine level. There was moderate demyelination, with fibrous gliosis, involving the medial longitudinal fasciculi, the central tegmental tracts, and the medial lemnisci. The red nuclei showed mild neuronal loss, with marked gliosis; the oculomotor nuclei and the substantia nigra were not affected. The basilar portion of the pons was not atrophic. In the medulla oblongata, the inferior olives showed pycnotic changes, with dense gliosis, but the number of neurons was not decreased. The vestibular nuclei showed mild rarefaction, with fibrous gliosis. At the lowest level of the medulla, the gracile and the cuneate, as well as the accessory cuneate, nuclei were involved. The spinal cord showed degeneration of the spinocerebellar tracts and the posterior columns. The lateral columns and the anterior horn cells were well preserved. The degenerative process in the cerebellum involved mainly dentate nuclei and their projections. The Purkinjé cells and the granular layer were spared. In the dentate nuclei, there was neuronal loss, with vacuolar and achromatic changes as well as grumose degeneration. There was dense glial proliferation from the hilus of the dentate nuclei up to the level of the red nuclei.

Discussion

Dentato-rubro-pallido-luysian atrophy is a disease in which the dentato-rubral (that is cerebellar efferent) system and the pallido-luysian segment of the extrapyramidal system degenerate together. It is comparable to olivo-ponto-cerebellar atrophy, in which the olivo-ponto-cerebellar and striato-nigral systems often degenerate concurrently.

In 1958, Smith *et al*² reported a case with ataxia and choreoathetotic movements under the title of *combined dentato-rubral and pallido-luysian degeneration*. The disease had an insidious onset, and took a slow progressive course. The predominant features were an ataxic gait and incoordination in the early stage of the illness, while in the later stage, choreoathetotic movements and grimaces became manifest. Myoclonus, or epileptic seizures, did not occur. In 1975 Smith⁶ reviewed the literature on dentato-rubro-pallido-luysian atrophy and concluded that a typical clinical course, if such there be, could not be clearly defined. This means that, from the clinical stand-point, dentato-rubro-pallido-luysian atrophy shows different symptoms even with essentially the same pathological changes. Recently

an increasing number of cases is being reported, particularly in Japan. On the basis of our experience we would like to point out some clinico-pathological characteristics.

Clinical aspects of dentato-rubro-pallido-luysian atrophy

We (Hirayama *et al*⁷), distinguished two clinical types of dentato-rubro-pallido-luysian atrophy: (1) the ataxo-choreoathetoid type, and (2) the pseudo-Huntington type. To these we have now added (3) the myoclonus-epilepsy type.

(1) *Ataxo-choreoathetoid type*: characteristic of this type are the case of Smith *et al*² and our cases Nos. 1, 2 and 4. In the early stages of the illness, ataxia is the prominent clinical feature: then, as the disease progresses, choreoathetoid movements become the main symptom. In other words, cerebellar signs are succeeded by extrapyramidal signs. There are no marked mental changes, nor is there any myoclonus, in these cases. Reviewing the literature, however, we notice some variations. For instance, Smith *et al*² did not describe disturbances of external ocular movements, which were commonly observed in our cases. Verhaart³ also mentioned upward gaze palsy and nystagmus. However, he did not mention choreoathetotic movements. Titica and van Bogaert¹ reported a case with personality changes, delusional ideas, and dementia in addition to choreoathetoid movements and ataxia. Neumann⁴ described gait disturbances and choreiform movements, disturbances of ocular movements, and seizures in her case 1. In spite of these variations, ataxia and choreoathetoid movement are nearly constant, with ataxia preceding the choreoathetoid movements. As far as our experience goes, the ataxia seen in this type of dentato-rubro-pallido-luysian atrophy is more pronounced in the lower extremities, but is no different from that seen in other types of spinocerebellar degeneration. The involuntary movements in our cases were slow and tonic, and rather close to athetoid or dystonic movements. Initially Smith *et al*² described such movements as "choreoathetoid", but later Smith⁶ changed his description to "dystonic, choreiform and ballistic". Other terms were used by different authors: "athetotic and hemiballistic" by Titica and van Bogaert,¹ and "choreiform" by Neumann.⁴ No cases, except case 1 of Neumann, had seizures and/or myoclonus.

In our cases, the disturbances of ocular movement had the nature of supranuclear conjugate palsy. Upward gaze palsy and horizontal nystagmus on gaze occurred in Verhaart's case, and in our cases 1 and 2. One of our cases (case 2) had monocular nystagmus. Other reported disturbances are "opso-

Table Pathological findings in dentato-rubro-pallido-luysian atrophy

	Ataxo-choreoathetoid form									
	Present cases			Titica & Van Bogaert (1946)	Verhaart (1958)	Smith et al (1958)	Neumann (1959)		Maeshiro et al (1980)	Sasaki et al (1980)
	Case 1	Case 2	Case 4				Case 1	Case 2		
Age/Sex	27M	28M	38M	48M	50M	66M	36F	60F	50F	21M
Heredity	+?	?	+?	+	?	—	?	?	—	—
Onset (yr)	15	12	21	44	41	58	22	51	45	20
Duration (yr)	12	16	17	4	9	8	15	10	5	1.5
Extrapyramidal symptoms	A	A	A	A, B	—	C-A	C	—	C-A-D	C-B
Purkinje cells	+	+	+	—	—	+	+	+	—	+
Dentate nuclei	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Red nuclei	(+)	+	+	+	++	+	+	++	+	(+)
Globus pallidus	+++	+	+++	+++	++	+++	+++	+++	+++	+++
Subthalamic nuc.	++	(+)	++	+++	+++	+++	+	(+)	+++	++
Caudate nuclei	—	—	—	+	—	—	++	—	—	—
Putamen	—	—	—	+	—	—	—	—	—	—
Subst. nigra	—	—	—	+	++	—	(++)	(++)	+	—
Tegmental atrophy	++	++	++	—	++	—	+	—	++	—
Med. long. fasc.	++	++	++	—	++	—	—	+	++	++
Central tegm. tr.	++	++	++	—	++	—	—	—	++	++
Pontine nuclei	—	—	—	—	—	—	—	—	—	—
Inferior olives	—	—	(++)	+	—	+	+	(++)	+	+++
Posterior columns	—	—	—	+	—	—	—	(+)	—	—
Posterior spinocerebellar tr.	+	+	—	—	—	—	—	—	—	+

A = athetoid movements, B = ballistic movements, C = choreic movements, C-A = choreo-athetoid movements, C-B = choreo-ballistic movements, C-A-D = choreo-athetoid-dystonic movements, + to +++ = grades of degeneration, ( ) = gliosis only.

clonus",² "slow eye movements" and "nystagmoid jerks".⁴ The mechanism of these disturbances of eye movement is unknown. They may perhaps be related to the severe brainstem atrophy which is commonly seen in this type of dentato-rubro-pallido-luysian atrophy. The pathological background will be discussed later. We believe these eye symptoms may be one of the essential characteristics of dentato-rubro-pallido-luysian atrophy, especially in the ataxo-choreoathetoid form.

(2) *Pseudo-Huntington type*: Our case 3 belongs to this type. We noted only slight cerebellar signs in the early stage, which was characterised by choreic movements, which persisted during the patient's downhill course. This type of dentato-rubro-pallido-luysian atrophy has been reported mainly in Japan, by Sakamoto *et al*,⁸ Kobayashi *et al*⁹ and Matsushita *et al*.¹⁰ Most of these cases were familial.

The case of Matsushita *et al*¹⁰

The patient was a 44-year-old woman. Her paternal grandmother, her father and one of her brothers seem to have shown the same symptoms. She had been healthy until the age of 25, when her gait became unsteady. The illness had progressed gradu-

ally. Personality changes appeared at age 37. Mental abnormalities became manifest, so that she had to be admitted to a psychiatric hospital at the age of 40. She was basically demented, and episodically fell into delirium with visual hallucinations. The prominent neurological features were involuntary movements, especially choreic movements involving the face and the distal parts of the extremities. Increased deep tendon reflexes were accompanied by clonus. Mild cerebellar signs, such as a wide-based gait, scanning speech, dysmetria and hypotonia were present. At the age of 44, the patient died of pneumonia, with the clinical diagnosis of Huntington's chorea.

Neuropathology: The most prominent lesions were seen in the dentate nucleus, in the globus pallidus and in their efferent systems. The dentate nucleus showed severe neuronal loss and grumose degeneration. Mild demyelination and fibrous gliosis were seen from the hilum of this nucleus to the red nucleus, through the superior cerebellar peduncles. The globus pallidus, especially its lateral segment, was also markedly degenerated, showing severe rarefaction of nerve cells and dense gliosis. Fibrous gliosis was also seen in the ansa lenticularis, in the H-field

	Pseudo-Huntington form				Myoclonic form (Naito et al 1982)					
	Present Case 3	Sakamoto et al (1971)	Kobayashi et al (1975)	Matsushita et al (1977)	Case 1	Case 2	Case 7	Case 12	Case 15	Case 16
Age/Sex	54M	40F	46F	44F	43M	23M	24F	27F	54M	20F
Heredity	+	+	+	+	+	+	+	+	+	+
Onset (yr)	35	24	20	25	30	13	10	19	38	13
Duration (y)	19	17	22	19	13	10	14	8	16	7
Extrapyramidal symptoms	C	C	C	C	—	—	—	—	C-A	C-A
Purkinje cells	+	—	+	+	+	+	+	+	+	+
Denate nuclei	+++	++	+++	+++	+++	+++	+++	+++	++	+++
Red nuclei	(+)	—	(+)	(++)	+	+	+	+	+	++
Globus pallidus	+++	++	+++	+++	++	+++	+++	++	+++	++
Subthalamic nuc.	(+)	—	—	—	—	++	+++	++	++	+++
Caudate nuclei	+	—	—	—	+	+	+	+	+	++
Putamen	—	—	—	—	+	+	+	+	+	++
Subst. nigra	—	—	—	—	—	—	—	—	—	—
Tegmental atrophy	++	—	—	—	++	+	+	+	++	+
Med. long. fasc.	—	—	—	—	—	—	—	—	—	—
Central tegm. tr.	—	—	—	—	+	—	—	+	—	—
Pontine nuclei	—	—	—	—	—	—	—	—	—	—
Inferior olives	—	—	(+)	—	++	+++	+++	++	+	+++
Posterior columns	—	—	—	—	—	—	—	—	—	+
Posterior spinocerebellar tr.	—	—	—	—	—	—	—	—	—	—

of Forel, and in the subthalamic nucleus.

Most of these reports speak of mental changes so severe that psychiatric care was necessary. Personality changes such as emotional lability, delusional ideas, and negativism were followed by dementia. Because of the manner of inheritance of the disease, the choreic movements and the mental disturbances, it is quite understandable that these cases should be diagnosed as Huntington's chorea. None of them, however, showed atrophy of the striatum or of the cerebral cortex. Seizures occurred in some cases, but no myoclonus. Disturbances of eye movements were not reported. In our case 3 the tegmentum was slightly atrophic, but the degeneration did not involve the medial longitudinal fasciculi, the central tegmental tracts, or the medial lemnisci.

(3) *Myoclonus-epilepsy type*: Naito and Oyanagi^{11 12} have reported on a degenerative form of myoclonus epilepsy, showing neuropathological changes indistinguishable from dentato-rubro-pallido-luysian atrophy. This case of Tanaka *et al*¹³ and Takahata *et al*¹⁴ belong to this type.

Case 1 of Naito *et al*:¹¹ age 20, female

On the father's side a strong tendency to convulsions was noted. Mental deterioration began at the age of 8 years. Convulsive seizures first occurred at 13.

Neurological examination revealed cerebellar symptoms such as dyssynergia, ataxic gait, and hypotonia. Epileptic seizures occurred at least once or twice a week. At the age of 16, myoclonic twitches appeared in the face, neck, and upper extremities. The choreoathetotic movements developed in the face, tongue, trunk, and extremities. The patient died of pneumonia at the age of 20.

Neuropathology: Severe degenerative changes, such as neuronal loss, myelin destruction, and dense gliosis, were noted in the external segment of the pallidum. The ansa lenticularis was atrophic and gliotic. The subthalamic nucleus showed severe neuronal loss and gliosis. Severe degenerative changes were observed in the dentate nuclei of the cerebellum, with grumose degeneration. The superior cerebellar peduncles were markedly gliotic. Mild degenerative changes were also seen in the cerebellar cortex, inferior olivary nuclei, anterior horns of the spinal cord, the reticular formation of the brain stem, and the cerebral cortex.

The clinical features of dentato-rubro-pallido-luysian atrophy show wide variations; on the other hand, the distribution of lesions in the cerebellar nuclei and in the pallidum, and in their efferent pathways, is relatively constant, with some quantitative variations. Cerebellar ataxia, extrapyramidal

disturbances and myoclonus-epilepsy are the most characteristic clinical features. In the course of the disease, one of these features may come to the fore, and later recede. Whether this fluctuating clinical course bears a direct relationship to the development of the lesions in place and time remains unknown. In an individual case at any one time one of the three types of disturbance dominates the clinical picture; and it is difficult to predict, from the pattern of the clinical findings, what will be the pattern of neuropathological changes.

Neuropathological aspects of dentato-rubro-pallido-luysian atrophy (table)

The histological changes of dentato-rubro-pallido-luysian atrophy are the usual degenerative changes, consisting in neuronal loss and glial reaction. The most constant and severest lesions are located in two systems, namely, the dentato-rubral and pallido-luysian systems. In our cases, however, tegmental atrophy and spinal cord lesions were also prominent. We would like to summarise some neuropathologically characteristic features of dentato-rubro-pallido-luysian atrophy.

(1) *Pathological changes in dentate nucleus and pallidum*

The dentate nuclei in all our cases were constantly and severely involved, with intense neuronal cell loss and dense gliosis. On the other hand the pathological changes in the pallidum were different in each case. In case 1, nerve cell loss in the pallidum was almost complete, especially in the outer segment. On the other hand, in case 2 changes in the pallidum were rather slight. The degenerative changes in the subthalamic nucleus also differed from case to case. It would appear from these findings that the dentato-rubral system is more severely and constantly affected than the pallido-luysian system. That the same is also true in the myoclonus-epilepsy type of dentato-rubro-pallido-luysian atrophy was suggested by Takahata *et al.*^{5 14}

(2) *Tegmental atrophy of the midbrain and pons*

In the ataxo-choreoathetoid form of dentato-rubro-pallido-luysian atrophy (cases 1, 2, 4), there is significant tegmental atrophy from the midbrain to the lower pons. Verhaart's³ and Maeshiro's¹⁵ cases showed the most severe tegmental atrophy, which was caused by degeneration of the superior colliculus, the central grey matter, and the reticular formation at midbrain level, and of the central tegmental tracts and reticular formation in the pons. These changes in the brain stem tegmentum are also found in the myoclonus-epilepsy type of dentato-rubro-pallido-luysian atrophy, but not in the

pseudo-Huntington type.¹² This suggests that tegmental atrophy is not an accidental but a characteristic finding in dentato-rubro-pallido-luysian atrophy, especially in our clinical types 1 and 3. On the other hand, our case 3 (type 2) showed no disturbances of ocular movement, and only slight tegmental changes. In the literature there is no description of tegmental atrophy in the pseudo-Huntington type. In our cases 1, 2, and 4, there was an upward gaze palsy, at least for a while; however, the expected lesions in the superior colliculi were not found in our cases. Furthermore in Verhaart's and in our three cases, there was marked degeneration of the medial longitudinal fasciculi. At present, it is difficult to identify any specific anatomical lesions as responsible for such disturbances of eye movements, partly because the clinical symptoms are not fixed but vary from time to time, and also because the pathological changes are complicated by multisystemic lesions.

(3) *Atrophy of the fastigio-vestibular system*

Using the serial section technique, we were able to demonstrate bilateral demyelination in the uncinate fasciculus and the juxtarestiform body in three of our cases (cases 1, 2, 3). According to the physioanatomical relationships between the fastigial and the vestibular nuclei, we considered these changes as important in the pathology of dentato-rubro-pallido-luysian atrophy. As far as we know, there is no literature on dentato-rubro-pallido-luysian atrophy which discusses these changes. (The possibility that these systemic changes are characteristic of dentato-rubro-pallido-luysian atrophy is a problem for further study.)

(4) *Friedreich's ataxia and dentato-rubro-pallido-luysian atrophy*

Demyelination of the spinocerebellar tracts was seen in our cases 1 and 2. Titica and van Bogaert¹ reported demyelination in the posterior columns and Sasaki *et al.*,¹⁶ and Naito and Oyanagi,^{11 12} observed it in both the posterior columns and the spinocerebellar tracts. Only two cases, reported by Verhaart³ and Maeshiro *et al.*,¹⁵ showed no spinal lesions.

André-van Leeuwen³ and van Bogaert¹⁷ reported a patient with pes cavus. The pathological findings in this case suggested a combination of dentato-rubro-pallido-luysian atrophy and Friedreich's ataxia. On the other hand, Oppenheimer¹⁸ mentioned that about 50% of cases of Friedreich's ataxia showed degeneration: not only in the spinal cord, but also in the pallidum and in the subthalamic nucleus. Cerebellar lesions, if present, were mainly in the dentate nuclei. According to Oppenheimer's

description, dentato-rubro-pallido-luysian atrophy and Friedreich's ataxia seem to have some similarities in the distribution of lesions, so that cases of dentato-rubro-pallido-luysian atrophy could have been described as "Friedreich's ataxia with atrophy of the dentate nucleus and brachium conjunctivum" in the past. The Friedreich pattern of spinal cord lesions may occur in other degenerative diseases, such as degenerative myoclonus epilepsy, dysynergia cerebellaris myoclonica, olivo-ponto-cerebellar atrophy, and even certain kinds of motor neuron disease. This suggests that this pattern of lesions is not specific, but could be a common pattern which appears in the spinal cord under certain pathological situations that affect both the cerebellum and the spinal cord simultaneously. Other changes, seen in case 1, are lateral column and anterior horn degeneration.

(5) Comparison of dentato-rubro-pallido-luysian atrophy with olivo-ponto-cerebellar atrophy

Olivo-ponto-cerebellar atrophy always affects the cerebellum and the brainstem, and also very often the extrapyramidal system. Hirayama *et al*^{19,20} recently claimed that extrapyramidal symptoms are not accessory but relatively constant and essential evidence of olivo-ponto-cerebellar atrophy. The extrapyramidal signs of olivo-ponto-cerebellar atrophy are essentially those of Parkinsonism, and they become manifest after the cerebellar signs, which are more prominent in the early stage of olivo-ponto-cerebellar atrophy. This appears to be in clear contrast to dentato-rubro-pallido-luysian atrophy, which has choreic, choreoathetoid or ballistic movements as extrapyramidal signs. On the other hand, the pathology of olivo-ponto-cerebellar atrophy involves mainly the pons, the cerebellar cortex, and the cerebellar white matter as well as the striato-nigral system, all of which are usually spared in dentato-rubro-pallido-luysian atrophy. Iizuka *et al*²¹ stressed this clear-cut difference between the two conditions: the cases of spino-cerebellar degeneration showing extrapyramidal symptoms belong to at least two clearly separate subgroups, presumably involving mechanisms based on metabolic changes. We have already reported that cases of olivo-ponto-cerebellar atrophy show decreased activities of dopamine-related enzymes, such as tyrosine hydroxylase, dopa decarboxylase, and dopamine β -hydroxylase, as is commonly seen in Parkinson's disease and also in striato-nigral degeneration.²² On the other hand, as far as we know, cases of dentato-rubro-pallido-luysian atrophy show no decreased activity of dopamine-related enzymes, whereas the GABA-related enzyme activities are very low, as in Huntington's chorea.²³ We do not know if these two

phenomena are essential pathognomonic changes in olivo-ponto-cerebellar atrophy and dentato-rubro-pallido-luysian atrophy, or if they are merely results of neuronal degenerative processes in these disorders. In any case, it seems to us important to investigate these degenerative diseases, not only from the clinico-pathological, but also from the metabolic point of view.

Conclusions

Four cases of dentato-rubro-pallido-luysian atrophy are reported with their clinico-pathological characteristics, as well as a review of the literature.

From the clinical standpoint, dentato-rubro-pallido-luysian atrophy may be divided into three types:

(1) *Ataxo-choreoathetoid type*: Cerebellar ataxia is manifest initially, and is replaced by choreoathetoid movements in a later stage.

(2) *Pseudo-Huntington type*: Choreic movements and dementia are always predominant, and cerebellar ataxia is mild or latent throughout the course.

(3) *Myoclonus-epilepsy type*: Prominent myoclonic twitchings, with generalised convulsive seizures accompanied by progressive mental deterioration, are the main features of this type.

In contrast with the mainly sporadic occurrence of type 1, types 2 and 3 are mostly familial. One of the main clinical symptoms represented in these three types dominates the clinical course in each type, but in the familial cases we can find cases of type 2 and type 3 in members of the same family.

Neuropathologically, the distribution and the nature of the degenerative changes in dentato-rubro-pallido-luysian atrophy are relatively constant, affecting principally the cerebellar deep nuclei and the pallidum, along with their efferent connections. In general, it seems that the dentato-rubral system is more severely and more constantly affected than the pallido-luysian system. Degeneration of the fastigio-vestibular system may also be a relatively constant phenomenon in dentato-rubro-pallido-luysian atrophy.

In the ataxo-choreoathetoid and in the myoclonus-epilepsy types, tegmental atrophy, extending from the midbrain to the lower pons, is significant, and is associated with clinical manifestations of oculomotor disturbances. In contrast, in the pseudo-Huntington type, which shows no ocular disturbances, tegmental atrophy is not seen.

Spinal lesions resembling those of Friedreich's ataxia may exist in all three types of dentato-rubro-pallido-luysian atrophy.

In future it will be important to investigate

dentato-rubro-pallido-luysian atrophy not only from the clinico-pathological but also from the biochemical point of view, especially in comparison with olivo-ponto-cerebellar atrophy and Friedreich's ataxia.

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