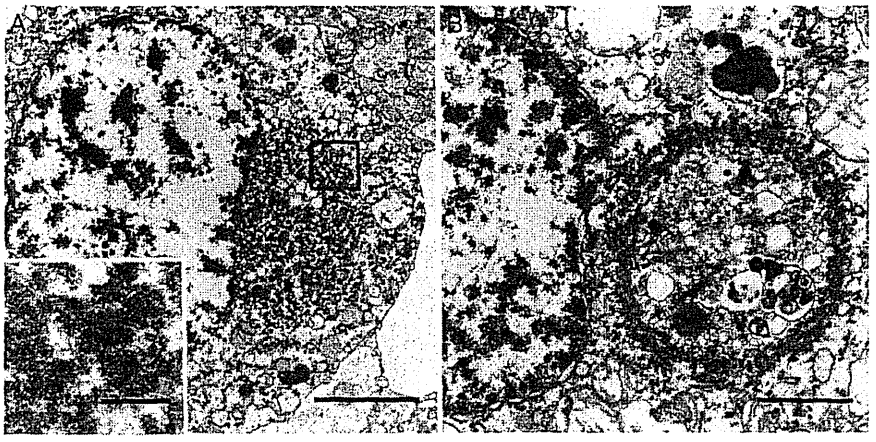

Fig. 4 (A) A ribosomal neuronal cytoplasmic inclusion (rNCI) is not membrane-bound and consists of aggregations of small electron-dense granular particles resembling ribosomal structures, and contains some degenerative organellae among ribosomes. Rough endoplasmic reticula (RER) are not related to the aggregations of the granules. Bar = 2 μm. Inset: higher magnification of granular particles. Bar = 0.5 μm. (B) A rNCI is globular in shape, the centers of which contain many degenerative organellae, surrounded by circular aggregations of ribosomes. Bar = 1 μm.

DISCUSSION

The most characteristic clinical symptoms in our case were psychomotor retardation in his infancy and epileptic attacks. Cerebellar ataxia and the mental and motor disturbances appeared and rapidly progressed in the second decade of his life. The neuroimaging study presented marked cerebellar atrophy at an early stage, but its atrophy was extended to the entire brain at an advanced stage. Abnormal CTG repeat expansion of SCA8 (23/127) was observed, but the symptoms were widespread to the whole brain which was different from those in previous autopsy reports of SCA8 that presented only symptoms in the brain stem and cerebellum.[1] The clinical symptoms of the cerebellar and motor neurons progressed concomitantly, and the pathological findings present cerebellar atrophy and neuronal loss of motor neurons (Fig. 2C,D). Because of these findings, we could not categorize this case as motor neuron disease or spinocerebellar ataxia involving motor neuron systems. However, based on clinical observations, the subjects with this abnormality of SCA8 mutation may either present no symptomatology[2,3] or be associated only with schizophrenia,[4] bipolar affective disorders,[4] Huntington phenocopy[5] or migraine.[6] This variable nature with inconsistent penetrance of the SCA8 mutation expansion suggests that corresponding phenotypes are influenced by factors other than this expansion itself. Thus, it remains unsolved whether the abnormal SCA8 mutation correlate with clinical phenotype in our case.

The most outstanding pathology was basophilic cytoplasmic inclusions, not reported to date, in the neurons. This inclusion was negative for Syn and AT8, but positive for Ub, P62 and faintly TDP43, superficially similar to basophilic inclusions (BIs) in TDP43-negative frontotemporal degeneration (FTD) or atypical amyotrophic lateral sclerosis (ALS).[7–9] The immunostain and digestion by RNAase demonstrated the content of RNA as a constituent. The negativity of FUS in our NCIs was distinct from BIs. The negativity of our NCIs for alpha-internexin, TIA and PABP-1 was different from BIs.

Ultrastructurally, these rNCIs were composed of ribosomes, not associated with the functional maturation of RER and filamentous structures,[7–9] which are different from BIs in FTD and ALS, and NCIs in multisystem atrophy (MSA) that consist of thick filamentous structures studded with electron-dense ribosome-like granules.[10] Furthermore, the distribution of BIs is quite different from that of rNCIs in our case in which they were widespread throughout all cerebral cortices, hippocampus and brain stem.[7–9]

Immunopositivity for 1C2 in NCIs may be explained by reverse transcription of the CTG repeat expansion, as in SCA8.[11,12] On the other hand, 1C2 immunorectivity related to the expansion of SCA8 mutation is nuclear in mice harboring the SCA8 expansion[11] or either nuclear[11] or cytoplasmic[1] in human autopsy cases. In any case, it is restricted to cerebellar Purkinje cells in reported cases,[1] and thus different from rNCIs in our case.

We reported novel neuronal cytoplasmic inclusions composed of ribosomal aggregations that were seen in the whole brain. Although 1C2-positivity of rNCIs might be induced by reverse transcription of the CTG expansion, it remains to be clarified how abnormal aggregations of ribosomes and extensive brain degeneration are related to the reverse or forward transcripts of the expanded repeat.

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A milestone on the way to therapy for MSA

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Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterised by parkinsonian, cerebellar, autonomic, and pyramidal symptoms; autonomic failure and either parkinsonism or cerebellar ataxia confirm a clinical diagnosis.[1,2] Pathological changes in MSA include cell loss, gliosis, and α-synuclein-positive glial cytoplasmic inclusions in the brain and spinal cord. However, an effective treatment that can modify the disease progression has not yet been established.

In this issue of *The Lancet Neurology*, Gregor Wenning and colleagues from the European MSA Study Group[3] report a multicentre-based prospective cohort study of 141 patients with MSA to identify predictive clinical factors for survival and deterioration of activities of daily living. They found that the parkinsonian variant of MSA and incomplete bladder emptying were significant predictors of survival. They also showed that a shorter disease duration at baseline and an absent levodopa response predicted rapid progression on the unified MSA rating scale (UMSARS), which was designed and validated by the European MSA study group as a quantitative outcome measure. Additionally, many aspects of the disease are well described, particularly a sample size estimation for an interventional clinical trial with 1-year assessment by UMSARS. This study confirmed and extended previous findings about the natural history of MSA[4,5] and, importantly, provides useful information not only for patient counselling, but also for planning of multicentre trials for novel drug development.

In MSA, several compounds have shown positive results in animal studies, cell culture studies, and exploratory clinical studies,[6,7] but there has been no drug with confirmed efficacy in large clinical trials. Developing a disease-modifying therapy for MSA has been hampered by several problems: limited natural history data; insufficient knowledge about the mechanisms of neuronal and glial cell loss; the scarcity of animal models that reflect human pathology; and the absence of tests to diagnose presymptomatic individuals or patients at very early stage of disease. However, by addressing the issue of natural history, Wenning and colleagues have opened new scientific frontiers for developing more reliable clinical trial designs, and, thereby, the possibility of new treatment for MSA.

Unlike for symptomatic relief treatments, such as levodopa for Parkinson's disease and cholinesterase inhibitors for Alzheimer's disease, a clinical trial design for disease-modifying therapies that slow or prevent neurodegeneration has not yet been established. Successful translational research of neurodegenerative diseases requires the identification of a target molecule that is closely involved in the pathogenesis of neurodegeneration. However, a more important aim is to establish a detailed prospective natural history with quantitative outcome measures, to define sensitive and validated disease-specific endpoints needed for effective clinical trials. On the basis of recent studies such as active immunisation with an amyloid β vaccine for Alzheimer's disease[8] and ligand-targeted therapies for spinal and bulbar muscular atrophy,[9] the duration of disease seems to be a crucial factor, with unequivocal effect on the outcome of the trial. The effects of disease-modifying therapies might be limited at even early symptomatic stages, because neuropathological changes progress during the presymptomatic stages. Furthermore, to develop novel neuroprotective therapies, study of earlier MSA cases, including patients with presymptomatic or premotor MSA, and identification of biomarkers to

diagnose the disease at these stages, will increase the chances of success of future clinical trials.[10]

In the medical care of patients with MSA, we need to establish the optimum time to introduce non-invasive positive pressure ventilation, tube feeding, and tracheostomy. Thus, the ability to predict several clinical milestones, such as those studied by Wenning and colleagues (gastrostomy, unintelligible speech, daily falls, inability to walk, and death), is valuable. There are some limitations in this study, such as a short follow-up period (2 years for UMSARS assessments), a low follow-up ratio (43 patients with total UMASRS data available at 24 months), and a small number of cases, which reduce the number of patients who reached each milestone. The causes of death were also not established. Longer-term follow-up periods and a higher follow-up ratio are needed to identify the overall progression and prognosis of MSA.

Although solving all the problems inherent in treating MSA is difficult, this study by the European MSA Study Group has greatly contributed to the establishment of many clinical features of MSA, and has shown the importance of a large multicentre study for documenting the prospective natural history of this rare type of neurodegenerative disorder. UMSARS will also play an important part as a clinical outcome measure in promoting future clinical trials of MSA. Further international co-operative studies will clarify the overall natural history, and enable potential therapeutic interventions to be initiated at an early stage.

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We declare that we have no conflicts of interest.

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Essential tremor: a unique diagnostic code in ICD-10-CM

The International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) ushers in, for the first time, a specific diagnostic code for essential tremor ("G25.0, essential tremor"). This milestone should not pass without comment.

Essential tremor is one of the most prevalent neurological diseases.[1] Although the core diagnostic feature is a kinetic tremor of the arms, other types of tremor (eg, postural, rest, intentional), additional motor features (eg, mild ataxic gait), and non-motor features (especially cognitive difficulties) have also been well described.[2] The disease is associated with progressive functional disability[3] and reduced quality of life.[4,5] In epidemiological studies, it has been linked with several neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease.[6]

The ICD provides alphanumeric codes for diseases and their diagnosis and treatment. This coding system was first initiated and compiled by WHO. Generally, these codes are enormously helpful in identifying and recording diseases.

Despite the high prevalence of essential tremor, estimated at 4–6% in individuals aged 65 years and older,[1] there is no specific ICD-9-CM diagnostic code.[7] In lieu of a disease-specific designation, the ICD-9-CM diagnostic code 333.1 ("essential and other specified forms of tremor") has been used as a coding category, resulting in the grouping together of a wide range of other disorders aside from essential tremor (eg, medication-induced tremor, psychogenic tremor, early Parkinson's disease, dystonic tremor) into the same coding category. For example, one study reported that of 964 patients with