Inoue et al., *Cogent Medicine* (2018), 5: 1434925
https://doi.org/10.1080/2331205X.2018.1434925

cogent medicine

NEUROLOGY | RESEARCH ARTICLE

An autopsy case of familial amyotrophic lateral sclerosis and dementia with p.R487H *VCP* gene mutation

Kimiko Inoue[1]*, Harutoshi Fujimura[1], Keiko Toyooka[1], Makito Hirano[2], Yusaku Nakamura[2] and Saburo Sakoda[1]

Abstract: We described an autopsied case of amyotrophic lateral sclerosis (ALS)-dementia with p.R487H mutation in the *VCP* gene. TDP-43-positive neuronal cytoplasmic inclusions (NCI), neuronal intranuclear inclusions (NII) and glial cytoplasmic inclusions were observed in the brain. The frequency of NCI was small but equal to that of NII, an atypical finding for *VCP*-related disorders. In contrast, the findings in the spinal cord and brainstem closely resembled those of sporadic ALS.

Subjects: Medical Genetics; Neurology; Dementia & Alzheimer's Disease

Keywords: familial amyotrophic lateral sclerosis; frontotemporal lobar degeneration; valosin containing protein; 43-kDa TAR DNA-binding protein (TDP-43)

Received: 22 January 2018
Accepted: 24 January 2018
First Published: 01 February 2018

*Corresponding author: Kimiko Inoue, Department of Neurology Toneyama National Hospital, Toneyama 5-1-1, Toyonaka, Osaka 560-8552, Japan
E-mail: kinoue@toneyama.go.jp

Reviewing editor:
Udo Schumacher, University Medical Center Hamburg-Eppendorf, Germany

Additional information is available at the end of the article

1. Introduction

Mutations in the *VCP* gene encoding valosin-containing protein were recently reported to be a cause of familial amyotrophic lateral sclerosis (ALS) (Johnson et al., 2010). *VCP* mutations are known to cause inclusion body myopathy with Paget's disease and frontotemporal dementia (IBMPFD) (Watts et al., 2004). Immunohistochemically, brain pathology of IBMPFD shows neuronal intra-nuclear inclusions (NII) with rare neuronal cytoplasmic inclusions (NCI) stained by 43-kDa TAR DNA-binding protein (TDP-43) (Neumann et al., 2007). Previous reports of ALS patients with *VCP* mutations (ALS-VCP) showed loss of motor neurons with Bunina bodies and TDP-43 accumulation identical to sporadic ALS cases (Ayaki et al., 2014; Johnson et al., 2010; Koppers et al., 2012); however, there were few pathological reports of ALS-dementia with *VCP* mutations (Spina et al., 2013).

1.1. Case history

The details of the clinical symptoms, family history and pedigree of the family, brain MRI and the DNA analysis were described in another report (Hirano et al., 2015). Briefly, a 61-year-old male

ABOUT THE AUTHORS

The authors of this article are the Neuropathological research group of the Toneyama National Hospital (Toyonaka, Japan). The group has been investigating neuropathology of the autopsied brains and biopsied specimens (brain tissue/peripheral nerve/muscle) from many hospitals in Osaka area since 2003 to confirm their clinical diagnosis or to search for the new findings. Our research focuses on the nervous systems of patients with neurodegenerative disorders by utilizing histochemical and immunohistochemical approaches.

PUBLIC INTEREST STATEMENT

This report is about a patient with a mutation in the *VCP* gene who died 12 years after onset of an ALS syndrome that evolved towards the end of the illness to include dementia. The clinical and genetic data have been published previously (*Neurobiology of Aging* 2015; 36:1604.e1–e6). This paper very briefly summarizes the clinical story and describes the pathology in the brain stem and spinal cord. Since the patient had a severe anoxic episode before death, the authors were unable to analyze the pathological changes in the cortex and the histopathological analysis is therefore limited to the brain stem and spinal cord, peripheral nerve and muscle.

noticed progressive weakness of the proximal upper limbs. When he was admitted to the hospital at the age of 65 years, he presented with bulbar palsy and tetraparesis with severe amyotrophy. One year later, he required tube feeding and artificial ventilation through tracheostomy. At 70-year-old, cognitive impairment and personality change were noted and he was diagnosed ALS-dementia. Brain MRI at the age of 72 years revealed frontotemporal lobar atrophy. He died of pneumonia one month after a global anoxic event at the age of 73.

2. Method

Autopsy was performed 1 h 9 mins post-mortem. Brain and spinal cord and some skeletal muscle (see below) were fixed with buffered 10% formalin, embedded in paraffin, prepared for routine and immunohistochemical examination. Anti-phosphorylated TDP-43 (anti-pTDP-43, Cosmo Bio, Japan), human PHF-tau (AT8, Innogenetics, Belgium) and ubiquitin (DAKO, Denmark) antibodies were used with a Ventana automated immunostaining instrument (Ventana, Tucson, AZ, USA). A part of a femoral nerve was fixed with buffered 2.5% glutaraldehyde, embedded in epon, cut into 1 µm semi-thin sections, and prepared for toluidin blue stain. Muscle specimens from the deltoid, iliopsoas and

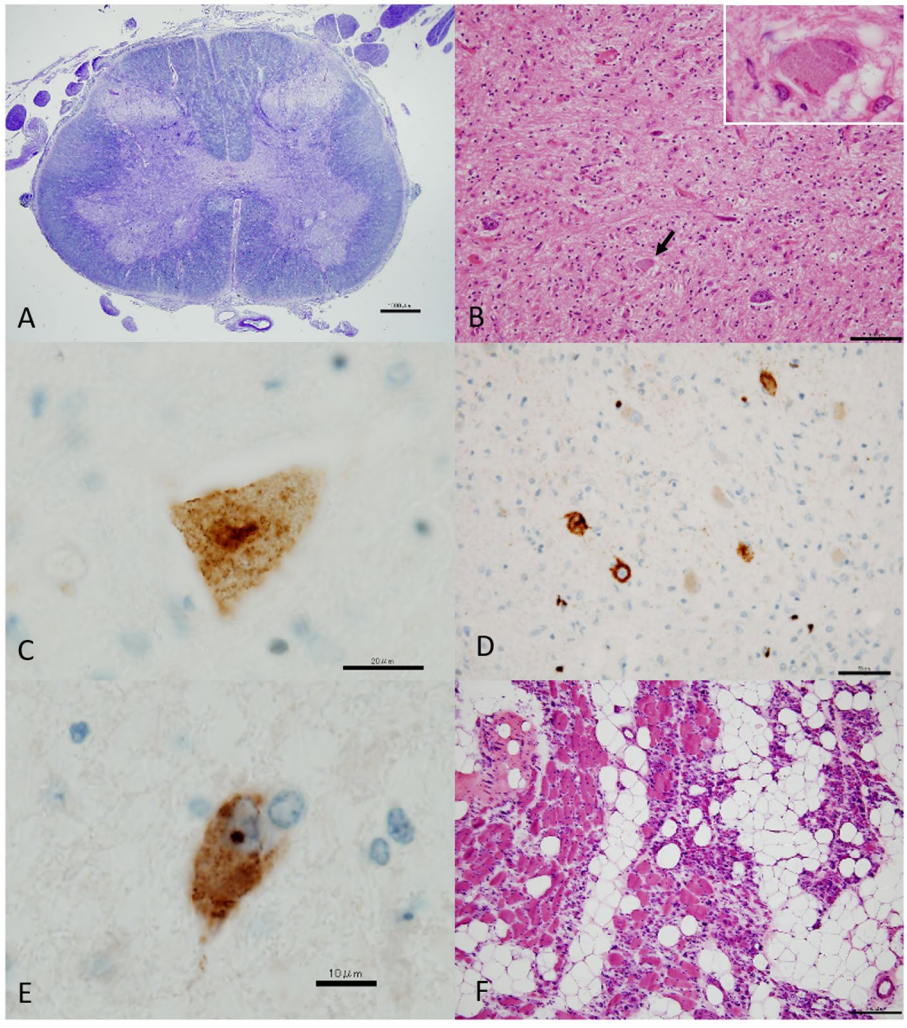

Figure 1. Neuropathological findings of the patient. (A) The lumbar cord of the patient showed loss of myelin and axons in the lateral and anterior corticospinal tracts. L4 level, KB stain. Scale bar, 2 mm. (B) Moderate neuronal loss and mild gliosis were found in the anterior horn of the lumbar cord. L4 level, H&E stain. Scale bar, 100 µm. Bunina bodies were found in the remaining motor neuron (arrow, inset). (C) pTDP43 immunoreactive NCI (Skein-like inclusions) were found in the remaining motor neuron. L4, pTDP43 immunohistochemical stain. Scale bar, 20 µm. (D) pTDP43 immunoreactive NCI and GCI were evident. Dystrophic neurites and dot-like form accumulation of pTDP43 were less frequently detected. Inferior olivary nucleus, pTDP43 immunohistochemical stain. Scale bar, 50 µm. (E) Some NII were found in the neurons of the midbrain and striatum. Mid brain tegmentum, pTDP43 immunohistochemical stain. Scale bar, 20 µm. (F) The examined muscles showed large group atrophy without myopathic change, nor rimmed vacuoles in the muscle fibers. Iliopsoas muscle, H&E stain. Scale bar, 200 µm.

quadriceps femoris were quickly frozen and prepared for routine, histochemical, and immunohistochemical examination with the same antibodies described above.

3. Results

The brain weight was 980 g. Because of macerated change of the cerebrum due to global anoxic damage, only the spinal cord, brainstem, a part of the cerebellum and basal nuclei were available for histological examination.

Microscopic examination revealed depletion of the lower motor neurons in the spinal cord and brainstem, associated with mild demyelination of pyramidal tracts (Figure 1(A) and (B)). Bunina bodies were observed in remaining motor neurons (Figure 1(B) inset). TDP-43 positive NCI and glial cytoplasmic inclusions (GCI) were observed in the motor neurons of the spinal cord, the brainstem motor nuclei, midbrain and striatum (Figure 1(C) and (D)). Some NII positive TDP-43 were also found in the neurons of the striatum and midbrain tegmentum (Figure 1(E)). There were no particular abnormal findings in the peripheral nerve except for decreased number of the axons. The examined muscles showed severely advanced group atrophy without myopathic change (Figure 1(F)).

4. Discussion

Both IBMPFD and ALS-VCP show muscle atrophy in their clinical course. González-Pérez et al. (2012) described a family with p.R191G *VCP* mutation, in which four family members had early to late stages of myopathy and fulfilled the clinical and electrophysiological El Escorial criteria for definite ALS. Autopsy reports showed neuronal loss of the anterior horn motor neurons in the spinal cord of IBMPFD patients without overt clinical motor neuron disease (Guyant-Marechal et al., 2006; Watts et al., 2007). On the other hand, in a previous pathological report of ALS-VCP (Ayaki et al., 2014) and in the present case myopathic change compatible with IBMPFD was not detected.

Another common symptom that IBMPFD and ALS-VCP share is frontotemporal dementia (FTD). Immunohistochemically, the features of IBMPFD with FTD were TDP-43 immunoreactive NII and dystrophic neurites with rare NCI in cerebral cortices (Neumann et al., 2007; Spina et al., 2013). Koppers et al. (2012) reported an autopsy of the brain of an ALS-VCP patient. They found a few TDP-43 positive NCI in the granular cells of the hippocampus and the neurons of the frontal and temporal cortices, which were identical to the sporadic ALS-dementia cases and occasionally found in ALS patients in whom dementia was not detected while they were alive.

The pathology in the spinal cord and brainstem of the present case closely resembled that of sporadic ALS. In the supratentorial area (partially examinable), TDP-43 immunoreactive NII, NCI and GCI were found. The frequency of NCI was small but equal to that of NII, a finding different from that reported on ALS-VCP or IBMPFD. However, it is possible that severe anoxic damage influences the metabolism of neurons and changes the immune-histological findings.

VCP related disorders have considerable clinical and pathological variation. For determination of the pathological correlation between clinical phenotypes and *VCP* gene mutation, accumulation of the patients and detailed pathological studies will be needed.

Acknowledgments
We greatly appreciate Mr. H. Yamada and Ms. C. Tada for their technical assistance in histological processing.

Funding
The authors received no direct funding for this research.

Competing interests
The authors declare no competing interest.

Author details
Kimiko Inoue[1]
E-mail: kinoue@toneyama.go.jp
Harutoshi Fujimura[1]
E-mail: hfujim@hosp.go.jp
Keiko Toyooka[1]
E-mail: ktoyooka@toneyama.go.jp
Makito Hirano[2]
E-mail: mahirano-neuro@umin.ac.jp
Yusaku Nakamura[2]
E-mail: nakamura@sakai.med.kindai.ac.jp
Saburo Sakoda[1]
E-mail: sakoda@toneyama.go.jp
[1] Department of Neurology, Toneyama National Hospital, Toneyama 5-1-1, Toyonaka, Osaka 560-8552, Japan.

[2] Faculty of Medicine, Department of Neurology, Sakai Hospital, Kinki University, Osaka, Japan.

Citation information
Cite this article as: An autopsy case of familial amyotrophic lateral sclerosis and dementia with p.R487H VCP gene mutation, Kimiko Inoue, Harutoshi Fujimura, Keiko Toyooka, Makito Hirano, Yusaku Nakamura & Saburo Sakoda, *Cogent Medicine* (2018), 5: 1434925.

References

Ayaki, T., Ito, H., Fukushima, H., Inoue, T., Kondo, T., Ikemoto, A., ... Morino, H. (2014). Immunoreactivity of valosin-containing protein in sporadic amyotrophic lateral sclerosis and in a case of its novel mutant. *Acta Neuropathologica Communications, 2*, 117. https://doi.org/10.1186/s40478-014-0172-0

Gonzalez-Perez, P., Cirulli, E. T., Drory, V. E., Dabby, R., Nisipeanu, P., Carasso, R. L., ... McKenna-Yasek, D. (2012). Novel mutation in *VCP* gene causes atypical amyotrophic lateral sclerosis. *Neurology, 79*, 2201–2208. https://doi.org/10.1212/WNL.0b013e318275963b

Guyant-Marechal, L., Laquerriere, A., Duyckaerts, C., Dumanchin, C., Bou, J., Dugny, F., ... Campion, D. (2006). Valosin-containing protein gene mutations: Clinical and neuropathologic features. *Neurology, 67*, 644–651. https://doi.org/10.1212/01.wnl.0000225184.14578.d3

Hirano, M., Nakamura, Y., Saigoh, K., Sakamoto, H., Ueno, S., Isono, C., ... Kusunoki, S. (2015). VCP gene analyses in Japanese patients with sporadic amyotrophic lateral sclerosis identify a new mutation. *Neurobiology of Aging, 36*(3), 1604-e1–1604-e6.

Johnson, J. O., Mandrioli, J., Benatar, M., Abramzon, Y., Van Deerlin, V. M., Trojanowski, J. Q., ... Ding, J. (2010). Exome sequencing reveals VCP mutations as a cause of familial ALS. *Neuron, 68*, 857–864. https://doi.org/10.1016/j.neuron.2010.11.036

Koppers, M., van Blitterswijk, M. M., Vlam, L., Rowicka, P. A., van Vught, P. W., Groen, E. J., ... van der Kooi, A. J. (2012). VCP mutations in familial and sporadic amyotrophic lateral sclerosis. *Neurobiology of Aging, 33*(4), 837-e1–837-e7.

Neumann, M., Mackenzie, I. R., Cairns, N. J., Boyer, P. J., Markesbery, W. R., Smith, C. D., ... Forman, M. S. (2007). TDP-43 in the ubiquitin pathology of frontotemporal dementia with *VCP gene* mutations. *Journal of Neuropathology and Experimental Neurology, 66*(2), 152–157. https://doi.org/10.1097/nen.0b013e31803020b9

Spina, S., Van Laar, A. D., Murrell, J. R., Hamilton, R. L., Kofler, J. K., Epperson, F., ... Ghetti, B. (2013). Phenotypic variability in three families with valosin-containing protein mutation. *European Journal of Neurology, 20*(2), 251–258. https://doi.org/10.1111/ene.2013.20.issue-2

Watts, G. D. J., Thomasova, D., Ramdeen, S. K., Fulchiero, E. C., Mehta, S. G., Drachman, D. A., ... Kimonis, V. E. (2007). Novel VCP mutations in inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia. *Clinical Genetics, 72*, 420–426. https://doi.org/10.1111/j.1399-0004.2007.00887.x

Watts, G. D. J., Wymer, J., Kovach, M. J., Mehta, S. G., Mumm, S., Darvish, D., ... Kimonis, V. E. (2004). Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. *Nature Genetics, 36*(4), 377–381. https://doi.org/10.1038/ng1332