

Original Paper

An autopsy case of Pick's disease and mini-review of the literature

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Abstract

The authors report a case of a Pick's disease which was at first diagnosed as residual schizophrenia. The patient received the diagnosis of Pick's disease three years later based on a CT scan which showed cerebral atrophy, and died from pneumonia about ten years after the onset. Autopsy revealed cerebral atrophy in the frontal and temporal lobes and histologically many Pick bodies were observed in the cortex and hippocampus. Pick bodies were examined immunohistochemically and ultra-structurally.

The necessity of Pick bodies to diagnose Pick's disease has been a source of contention since this disease was first named, so Pick's disease continues to be investigated by new methods. From image-based method of diagnosis, new clinicopathological diagnostic criteria for frontotemporal dementia was proposed. Additionally, Pick's disease is a member of the classification of diseases known as tauopathy, based upon the concept of abnormal protein accumulation in the brain. The recent classification should be referred to make accurate diagnosis to this kind of diseases.

Key Words: Pick's disease, tauopathy, autopsy

Introduction

Pick's disease is a relatively rare progressive dementia with symptoms including personality changes, aphasia and others. This disease is neuropathologically characterized by Pick bodies, argentophilic globes in neuronal cytoplasm. However it is controversial whether the presence of Pick bodies is necessary to diagnose as Pick's disease. Its diagnoses are commonly made without autopsies, so cases of Pick's disease with confirmed Pick bodies are extremely rare. Because of the advancing methods of image-based diagnosis and immunohistochemical technique, the classification of dementia containing Pick's disease has been restructuring in the last ten years. Here we report an autopsy case of Pick's disease with Pick bodies, which were examined with immunohistochemical and ultra-structural methods, and review the literature

about Pick's disease.

Clinical Summary

A 59-year-old male had been hospitalized several times with the diagnosis of residual schizophrenia. There was no family history of neurologic or psychiatric disease, including dementing disorders. His character traits had been quietness, stubbornness, and selfishness, and he often changed jobs throughout his life. When he was 50 years old, after divorce he began to show the tendency to stay indoors, and once attempted suicide. At the hospital which he visited after the suicide attempt, the diagnosis of residual schizophrenia was made. When he was referred to Shin-Abuyama Hospital at the age of 53, flexion contracture of both elbows was observed. A CT scan of the brain disclosed symmetrical atrophy at the frontotemporal lobar and the lateral ventricles

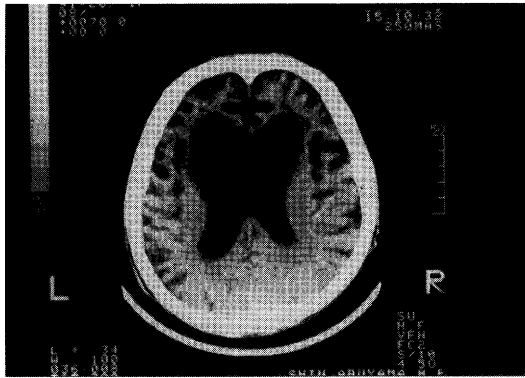


Fig.1 CT scan of the brain showed symmetrical atrophy at the frontotemporal lobar and the dilated lateral ventricles

were dilated (Fig. 1). Tetraplegia in flexion was observed and gradually increased in severity, and later apallisches syndrome also occurred. These symptoms and the cerebral atrophy suggested the third period of Pick's disease.

One year after being released, he was again admitted for pneumonia, from which he died. Autopsy was limited to examination of the brain.

Autopsy Findings

The postmortem examination was begun eight hours after death. The body weight was 53kg, the height was 165cm. The brain weighed 1,140g and showed severe atrophy of the frontal and temporal lobes with relative preservation of the parietal and occipital lobes which are edematous (Fig. 2a). The cerebellum was unaffected. Transversal section of the cerebrum confirmed the lobar atrophy and showed dilation of both frontal horns (Fig. 2b). The cerebrospinal liquid was yellow and transparent.

Histologically, the number of neurons was reduced and a marked gliosis developed in the atrophic portion of the cortex. Some of the remaining cortical neurons contained argentophilic globules: Pick bodies. The Pick bodies were predominant especially within the hippocampus (Fig. 3). In some of the remaining neurons the nucleus became pyknotic, and in the cytoplasm of other neurons many eosinophilic granules were observed. In the white matter gliosis stood out prominently. The Pick bodies demonstrated positive expression when stained with tau protein antibody (Tau Ab-3, rabbit polyclonal antibody,

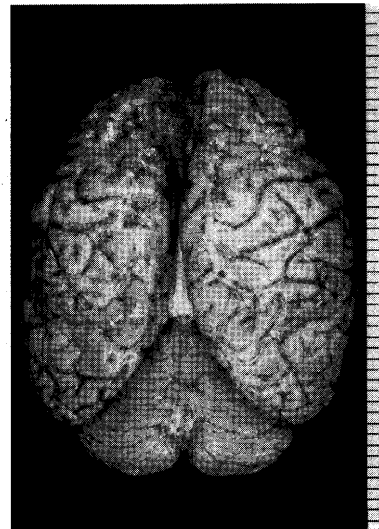


Fig. 2a There is severe atrophy in the frontal and temporal lobes (1,140g)



Fig. 2b Transversal cut showing gross frontal and temporal atrophy with enlargement of ventricles

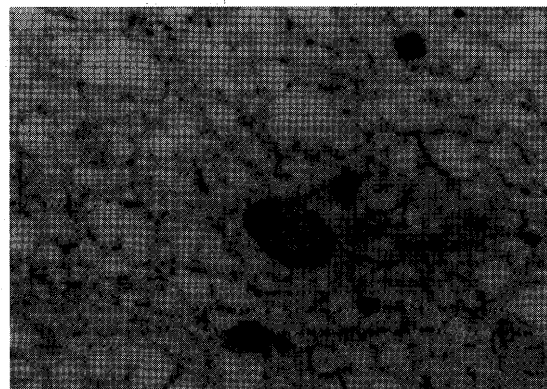


Fig. 3 A well-defined neuronal cytoplasmic inclusion: Pick body (Bodian, ×400)

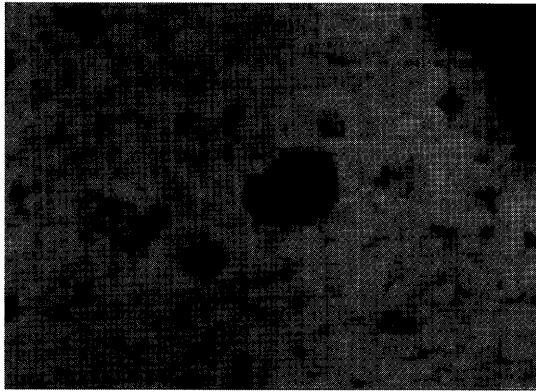


Fig. 4 The Pick body stained with tau protein antibody ($\times 400$)

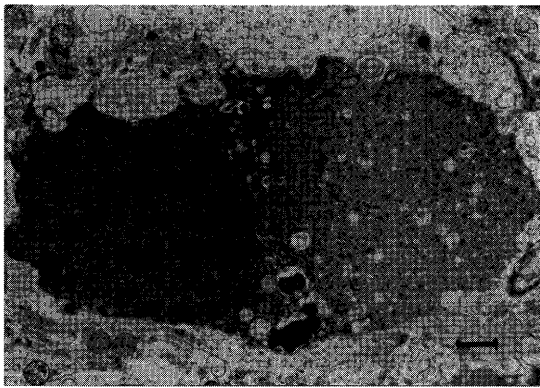


Fig. 5a Electron microscopy of neurons with a Pick body (bar: 10mm)



Fig. 5b A cytoplasmic accumulation of filaments (bar: 1mm)

Neomarkers, California, USA) by immunohistochemistry (Fig. 4). Besides Pick bodies there were a lot of materials which showed a positive signal for tau protein antibody in the neurons and the interstitium. Electron microscopy of neurons with a Pick body (Fig. 5a) showed a cytoplasmic accumulation of fila-

ments (Fig. 5b).

From the clinical and pathological findings we made the diagnosis of this case as Pick's disease.

Discussion

The case we reported here was a classical Pick's disease with Pick bodies neuropathologically, however the clinical course was different from typical cases at the onset and it had been difficult to diagnose until cerebral atrophy emerged. Generally Pick's disease is difficult to clinically differentiate from Alzheimer's disease and other forms of progressive dementia. In addition there has been some disagreement about the definition; its criteria and classification are still being discussed. Here we review the history and recent report of this disease.

In 1892, Arnold Pick, a professor of psychiatry at the University of Prague, reported a case of dementia (Girling et al. 1994) which was later named Pick's disease by Onari and Spatz (1926). He described its gross pathological features but not its histological features. The microscopic characteristics of this disease, the presence of argentophilic globes in neuronal cytoplasm, was described by Alzheimer several years later (1911). There has thus been controversy whether Pick bodies must be present for Pick's disease to be diagnosed. In contrast to European and American neuropathologists, Japanese neuropathologists commonly diagnose Pick's disease even without Pick bodies. Kosaka et al. (1991) reported 41 autopsy cases of Pick's disease, in which Pick bodies were detected only in 11 cases (26.8%).

The Lund and Manchester Groups (1994) proposed clinicopathological diagnostic criteria for frontotemporal dementia (FTD). According to this criteria, Pick's disease is classified as one of a broad category of FTDs, which is classified into three groups: a frontal lobe degeneration type, a Pick type, and a motor neuron disease type.

On the other hand since the establishment of the immunohistochemical method, Pick's disease has been also investigated immunohistochemically for several proteins. Iseki et al. (1998) discovered the existence of phosphorylated tau accumulation in Pick bodies and of ubiquitin-positive tau-negative neuronal and neuritic inclusions in atypical Pick's disease

without Pick bodies. Now noting the abnormal proteins accumulating in the central nervous system, Pick's disease is categorized into tauopathy. Tau is a collection of microtubule-associated proteins expressed from a single gene on chromosome 17. Originally Spillantini and et al. (1997) reported Frontotemporal Dementia with Parkinsonism-17 (FTDP-17) as a tauopathy. Now the term "tauopathy" is a heterogeneous group of neurodegenerative disorders sharing inclusions of insoluble hyperphosphorylated tau protein in neurons or sometimes in glial cells. Examples of tauopathic disorders include Alzheimer's disease, progressive supranuclear palsy, and corticobasal degeneration, as well as Pick's disease. Zhukareva et al. (2002) characterized the pathological tau of Pick bodies biochemically, and divided Pick's disease into three categories according to the isoforms of the tau protein: 1) predominantly three microtubule-binding repeats tau (3R-tau), 2) predominantly four microtubule-binding repeats tau (4R-tau), and 3) both 3R- and 4R- tau isoforms. Another group (Mori et al. 2002) also investigated synucleins which accumulate in neurons and glia of neurodegenerative disorders including Parkinson's disease, dementia with Lewy bodies and other so called synucleinopathies. And they showed that Pick bodies are positive for alpha- and beta-synucleins but not gamma-synuclein. The origin and fundamental cause of Pick's disease has not yet been conclusively determined.

Several neurodegenerative diseases are still difficult to diagnose from clinical features, and even autopsies cannot always reveal their pathogenesis. However in the present case the autopsy was able to show that this Pick's disease with uncommon clinical course was a classical Pick's disease with Pick bodies. Although the number of autopsies is decreasing due to the progress of image analysis such as NMR (Nuclear Magnetic Resonance) and PET (Positron Emission Tomography), in the realm of the central nervous system it is still necessary to investigate the accumulated materials for the elucidation of some neurodegenerative diseases.

Finally, we introduce some sites on the Internet which give information about Pick's disease to the public:

- 1) The Association for Frontotemporal Dementias
<http://www.ftd-picks.org/>

- 2) The Pick's Disease Support Group
<http://www.pdsg.org.uk/>
- 3) NINDS (National Institute of Neurological Disorders and Stroke) Pick's Disease Information Page
http://www.ninds.nih.gov/health_and_medical/disorders/picks_doc.htm
- 4) A project of The Rotary Club of Santa Monica and Center for Healthy Aging
http://www.helpguide.org/elder/picks_disease.htm

Not only these official sites but also several private sites exist in English, however there are not so many Japanese sites for patients:

- 5) The Tokyo Metropolitan Institute for Neuroscience
<http://www.tmin.ac.jp/>
- 6) Information service about an intractable disease of the nervous system and a muscle
<http://www.saigata-nh.go.jp/nanbyo/>

There are few sites specifically about rare diseases such as Pick's disease in Japanese. Information on even diseases with severe prognoses should be made available to the patients and families. We hope that more sites which give this kind of accurate and intelligible information will be established in Japanese.

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