—Review—

Changes in Neurological Diseases in the Last Half Century

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In 1953, I came to New York. After I trained in neuropathology under Professor Harry M. Zimmerman at Montefiore Medical Center, I became a neuropathologist, eventually succeeding Dr. Zimmerman as the head of the Division of Neuropathology in 1965. During these years, remarkable advancement of scientific technology, such as application of electron microscopy, tissue culture, immunohistochemistry, CT, MRI, and molecular genetics, has contributed to numerous discoveries in neurological diseases. In addition, various new diseases were recognized in this period. Our experience in the neuropathology of AIDS in the Bronx, New York and neurodegenerative diseases on the island of Guam is presented in this review.

1. AIDS

When I attended the Annual Meeting of the American Neurological Association in September, 1982, I heard a presentation on the neurological disorders associated with AIDS (Acquired immune deficiency syndrome) for the first time. The outbreak of many AIDS patients with unusual opportunistic infections and lymphoma involving the nervous system was reported from two institutions in Manhattan, New York and Los Angeles respectively. This paper shocked the audience. However, I thought it was a special event only limited to homosexual males in certain regions. I never dreamed I would make a neuropathological diagnosis of AIDS at Montefiore Medical Center in the Bronx. I was soon proven wrong. In December of the same year, a 32-year-old female was admitted due to a headache that lasted 1～2 days followed by a convulsion. A CT scan disclosed a lesion in the left parietal lobe. Clinically glioma, herpes encephalitis, and infarct were considered and a brain biopsy was performed. Light microscopic examination revealed a definite lesion but final diagnosis of *Toxoplasmosis* was achieved by demonstration of the organisms with electron microscopic examination. Further work-up established the first diagnosis of AIDS in our institution.

Thereafter, an increasing number of AIDS patients appeared in many cities in the U. S. According to a report by the CDC (Center for Disease Control), there was steady and rapid rise in the number of patients every year since the first AIDS case was found in 1981. New York City had the greatest number of documented cases: one-third of the AIDS cases in the country. Sixty percent of these patients were reported to be dead. The number of patients reached approximately 5,000 in the U. S. and 7,500 in the world. In Japan there were 30 patients reported, including 11 deaths. Among the AIDS patients in the U. S., the majority were homosexual men followed by intravenous drug abusers. Infections due to the blood transfusion for hemophilia and other factors were far less common. A retrovirus was discovered as the organism causing AIDS and it was named HIV (human immunodeficiency virus).

Montefiore Medical Center is in the Bronx, New York, where many AIDS patients have been diagnosed. The number of autopsied cases reached 100 by December, 1987, only five-and-a-half years after the first case in 1982. Analysis of the postmortem material disclosed findings essentially similar to those reported elsewhere, but we recognized certain unexpected features in our series. The vast majority of cases were men between the ages of 20 and 40 years old, especially 30 year olds, which matched reports from other geographic locations. It is noteworthy that there were 28 female patients and 8 infants and children under 10 years old in our series. At top risk were the intravenous drug abusers who contracted AIDS twice as fre-

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quently as homosexual men and occupied 41% of the AIDS population.

Among neuropathological findings associated with AIDS, inflammatory lesions caused by opportunistic infections caught our attention first. It was found in approximately 1/3 of our autopsied cases. *Cryptococcosis*, *toxoplasmosis*, and *cytomegalovirus* infections were by far the most common in our series, followed by progressive multifocal leukoencephalopathy and *herpes zoster*. Malignant lymphoma was present in 10% of our cases. Most of the lymphoma found in adults was primary lymphoma, while metastatic secondary lymphoma was observed in children. In some cases cerebral infarct and hematoma were also recognized. With further examination of many cases, progressive dementia was recognized clinically in addition to the focal lesions associated with opportunistic infections in the central nervous system. This was termed AIDS-dementia complex, which occurs in 2/3 of AIDS patients. It became apparent that HIV affects not only T4 lymphocytes (lymphotropic), but also brain parenchyma (neurotropic). HIV is found mostly in multinucleated giant cells, mononuclear cells, and macrophages, as well as in extracellular space.

AIDS was not listed in the dictionary 20 years ago. Now AIDS is one of the most famous infectious diseases affecting the human population world-wide. Extensive efforts have been directed to control this serious disease and there has been some success in preventing its further spread.

2. Amyotrophic lateral sclerosis and Parkinsonism-dementia complex on Guam

Amyotrophic lateral sclerosis (ALS) is an age-related neurodegenerative disease that affects the motor nervous system. It is one of the most well-known as Alzheimer's disease and Parkinson's disease. With the increase of the aged population in this century, these ailments have become a growing problem not only in medicine, but also in human society.

The island of Guam in the Western Pacific Ocean represents a geographic isolate with a phenomenal incidence of fetal degenerative neurological diseases. Among these the most well known entity is ALS, which at one time affected 5～10 percent of the adult Chamorro population on the island. This is 100 times more than those affecting other populations in rest of the world. In 1959, I was sent to Guam as a visiting scientist of NIH (the National Institute of Health) and engaged in a clinico-pathological investigation of ALS for 13 months. During this period I examined 57 ALS patients including 26 newly diagnosed patients. Furthermore, I was able to confirm the diagnosis of ALS neuropathologically on 97 ALS cases autopsied during the 4-year period from 1957 to 1960. All the Chamorro ALS cases revealed typical neuropathological features of classic ALS. However, it was remarkable to observe Alzheimer's neurofibrillary changes in certain areas of the central nervous system. These changes are usually not found in ALS elsewhere.

In addition to finding cases of ALS, we recognized cases of Parkinsonism in many Chamorro patients. These cases were often associated with progressive dementia. Since the classic teaching about Parkinson's disease was that the patients were usually not demented, a new term was coined to describe the clinical entity as Parkinsonism-dementia complex (PDC) on Guam. Some of the PDC patients had additional symptoms and signs of ALS. Neuropathological examinations were performed on 63 PDC cases from 1958 to 1964. Prominent cerebral atrophy, especially in the temporal lobes, was observed. The substantia nigra and locus ceruleus were severely atrophied and depigmented in all cases. Histologically areas affected in Parkinson's disease were all involved, but to a much more severe degree. These included substantia nigra, locus ceruleus, nucleus basalis of Meynert, and dorsal motor nucleus vagus. In addition, the cerebral cortex, especially the temporal lobes, was also severely affected. Marked neuronal loss was evident in these areas.

The remarkable finding in PDC was the presence of numerous Alzheimer's neurofibrillary changes in a selective topographic pattern. The vulnerable neurons were found in the entorhinal cortex, the pyramidal neurons of the Sommer's sector and its adjacent area in Ammon's horn, the subiculum, the amygdaloid nucleus, the nucleus basalis of Meynert, the pigmented neurons in the substantia nigra and locus ceruleus, the dorsal raphe nucleus, and the reticular formation of the brain stem. The motor neurons, such as the large anterior horn cells in the spinal cord, were rarely affected, while Purkinje cells were not affected with Alzheimer's neurofibrillary changes at all. A similar topographic distribution of Alzheimer's neurofibrillary changes was observed in Chamorro ALS, but usually to lesser extent. It is noteworthy

that even the adult Chamorro without known ALS and PDC revealed Alzheimer's neurofibrillary changes, although in general much less in these control Chamorro cases than in PDC patients. Two other intraneuronal structures, granulovacuolar degeneration and eosinophilic rod-like structures (Hirano bodies), were observed in the Sommer's sector of the brains studied on Guam. Both are features of aging and also are numerous in certain diseases such as Alzheimer's disease and Pick's disease. The Lewy bodies' characteristic marker for Parkinson's disease was usually absent and rarely seen in the midbrain of 10% of the PDC cases. They are associated with Alzheimer's neurofibrillary change-bearing neurons in the vicinity. Even neurons containing both Lewy bodies and Alzheimer's neurofibrillary changes were observed in the midbrain of two cases.

An interesting finding in the Guam cases is the lack of senile plaques in spite of the presence of numerous Alzheimer's neurofibrillary changes. In contrast, both Alzheimer's neurofibrillary changes and senile plaques are abundant in cases of Alzheimer's disease. In spite of the absence of senile plaques, the fine structures of Alzheimer's neurofibrillary changes in Guam patients are identical to those observed in Alzheimer's disease. The finding in the Guam material of neurofibrillary changes without associated senile plaque called attention to many other conditions that have neurofibrillary accumulation without associated senile plaque formation. Among these are progressive supranuclear palsy, corticobasal degeneration and frontotemporal dementia and parkinsonism linked to Chromosome 17 (new group of tauopathy).

Since our clinicopathological studies based on 120 Chamorro patients on Guam (57 ALS and 63 PDC) autopsied during the 6-year period, over a quarter century has passed. During this period a dramatic decline in the incidence of ALS on Guam has been reported. ALS is a fetal disease of unknown etiology. There is no known specific treatment to cure the patient or prevent the disease. In spite of the extensive investigation of Guam diseases including genetic study, no definite cause is established. There has been a dramatic improvement in the native Chamorro standard of living after World War II. Changes in the aspects of exposure to putative environmentally-based etiologic agents have been suggested as an explanation the marked decline in ALS on the island.

The report of the high incidence of ALS on Guam was confined to the Chamorro population in which familial aggregation was common. Therefore, genetics was considered the underlying factor. In 1955, Kurland and Mulder surveyed the literature on familial ALS for the past 100 years outside Guam. They called attention to the occurrence of familial ALS in approximately 5～10% of the ALS cases. In 1976, we observed Lewy body-like inclusions in the anterior horn cells of certain familial ALS cases from the United States. These Lewy body-like inclusions were not observed in any Guam ALS cases before 1976. In 1993, Rosen et al reported that mutation of the Cu/Zn superoxide dismutase (SOD1) gene, located on chromosome 21q, is associated with certain familial forms of ALS. In approximately 1/4 of familial ALS, the gene defect has been identified. Immunohistochemical study revealed strong SOD1 positive reaction with the Lewy body-like inclusion and considered being a marker of this type of familial ALS. Transgenic mice carrying the SOD1 mutation have been developed to research the pathomechanism of this motor neuron disease.

At the time we had observed the Lewy body-like inclusions in the anterior horn cells, the genetic information was not yet known. Now with Rosen et al's discovery and immunohistochemical demonstration of SOD1 positive reaction on the Lewy body-like inclusions, we can connect morphology and genetics in this partial form of familiar ALS. In no cases in Guam has this SOD1 gene defect been identified. The lack of SOD1 gene defects in Guam ALS agrees well with the absence of the Lewy body-like inclusions.

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