Neurofibrillary Tangles in Patients with Down’s Syndrome: 
A Light and Electron Microscopic Study

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Summary. Two older patients with Down’s syndrome and widespread neurofibrillary tangles and senile plaques were studied by light and electron microscopy. The ultrastructural demonstration of twisted tubules verified the assumption that the tangles encountered in these patients were Alzheimer’s neurofibrillary tangles. Despite the morphological evidence of Alzheimer’s disease, neither of these patients were clinically demented.

Key words: Down’s Syndrome — Alzheimer’s Disease — Neurofibrillary Tangles — Twisted Tubules.

Many authors (Struwe, 1929; Bertrand and Koffas, 1964; Jervis, 1948; Malamud, 1964; Solitaire and Lamarche, 1966; Neumann, 1967; Olson and Shaw, 1969; Haberland, 1969) have reported the presence of neurofibrillary tangles and/or senile plaques in patients with Down’s syndrome who were over the age of 35 years. These changes are generally considered to be histopathological evidence of Alzheimer’s disease. Malamud (1957) makes the generalization that “among patients diagnosed as Mongolian idiots who have survived to middle age, it is common to find clinical and pathologic manifestations of Alzheimer’s disease”. Electron microscopic studies in recent years have shown that Alzheimer neurofibrillary tangles are composed of twisted tubules with a maximal diameter of 220 Å and periodic constrictions at intervals of 800 Å where the diameter is only about 100 Å. While it has been tacitly assumed that the tangles in the older individuals with Down’s syndrome are Alzheimer neurofibrillary tangles composed of these distinctive twisted tubules, aggregates of other types of neuronal fibrous proteins, especially neurofilaments, would be indistinguishable by light microscopy (Schochet, 1972).

This report presents the light and electron microscopic findings from two older individuals with Down’s syndrome.
Material and Methods

Case 1. This 40 year old white woman had been born when her mother was 45 years old. The patient was able to walk at 2 1/2 years and talk at 3--4 years of age. She had attended school until the fifth grade when she was withdrawn because of her slow learning ability. She could read a newspaper but was unable to make change. She lived at home until 2 1/2 years before her death. She was alleged to have declined mentally during the last 6 months of her life but was not regarded as demented. She died from septicemia, pneumonia and adenocarcinoma of the rectum.

At autopsy the brain weighed 1000 g and showed severe, diffuse atrophy with narrowed gyri and widened sulci. There was symmetrical dilatation of the ventricular system. Microscopically there was a marked reduction in the neuronal populations of the isocortex, allocortex and basal ganglia. Numerous neurofibrillary tangles and senile plaques were present throughout the cerebral cortex (Fig. 1a, b). The hippocampi also contained numerous granulovascular bodies and scattered Hirano bodies. In the basal ganglia, the amygdalae contained numerous senile plaques and the globus pallidus contained heavy, predominantly perivascular, mineral deposits. Occasional globose neurofibrillary tangles were present in mesencephalic nuclei.

Case 2. This 38 year old white woman had been born when her mother was 25 years old. The patient appeared mongoloid at birth and was found to be severely mentally retarded by the age of 3 years. She lived at home until 18 when she was institutionalized. During the last month of her life she had frequent colds, was unable to perform her daily tasks as well and was hyperkinetic but was not regarded as demented. She died from massive aspiration and pneumonia. Chromosomal karyotyping revealed trisomy G.

At autopsy the brain weighed 1130 g and was atrophic with especially small but symmetrical superior temporal gyri. Microscopically there was a marked reduction in the neuronal population of the isocortex, allocortex and basal ganglia. Neurofibrillary tangles (Fig. 1c) and senile plaques were present throughout the cortex but were especially numerous in the hippocampi. The globus pallidus contained heavy, predominantly perivascular, mineral deposits.

For electron microscopy, portions of formalin fixed hippocampi from both cases were postfixed in phosphate buffered 2% osmium tetroxide, dehydrated and embedded in epoxy resin. Sections 2 μ thick, stained with alkaline toluidine blue, were examined by light microscopy in order to select blocks containing neurofibrillary tangles for thin sectioning. The thin sections were stained with uranyl acetate and lead citrate prior to examination in a Philips EM 300 electron microscope.

Results

Virtually identical fine structural features were found in the hippocampi from both patients. Although the tissues showed autolytic changes, the detailed ultrastructure of the neurofibrillary tangles and senile plaques could be ascertained readily. The neurofibrillary tangles consisted of various sized compact skeins of fibrillary material (Fig. 2a). Higher magnification showed that the tangles contained only twisted tubules (Fig. 2b). These had a maximal diameter of 220 Å and at intervals of 800 Å, constricted to about 100 Å. When seen in cross-section, the tubules had a circular profile. Most of the neurons harboring the tangles also contained abundant lipofuscin.

The senile plaques consisted of groups of swollen neurites containing numerous lamellar dense bodies, mitochondria and short lengths of twisted tubules. In an extracellular location among the abnormal neurites were deposits of amyloid consisting of thin 70 Å wide tubules (Fig. 2c). Astrocytes characterized by their 70 Å filaments were present about the periphery of the plaques.