Detection of Lewy Bodies in Trisomy 21 (Down’s Syndrome)


ABSTRACT: The presence of cortical senile plaques and neurofibrillary tangles sufficient to warrant a neuropathological diagnosis of Alzheimer’s disease is well established in middle-aged individuals with Trisomy 21 (Down’s syndrome). In contrast a relationship between Down’s syndrome and Lewy bodies, one of the major neuropathological features of Parkinson’s disease, has not been previously reported. In a cliniconeuropathological survey of 23 cases of Down’s Syndrome, two patients, aged 50 and 56 years respectively, were found to have Lewy body formation in the substantia nigra in addition to cortical Alzheimer-type pathology. Neither case showed significant substantia nigra neuron loss although locus coeruleus loss was present in both. Since substantia nigra Lewy bodies are a characteristic neuropathological feature of idiopathic Parkinson’s disease, their occurrence in cases of Down’s syndrome with evidence of Alzheimer-type pathology supports an aetiological connection between Parkinson’s disease, Alzheimer’s disease, and Down’s syndrome; and suggests that common pathogenic mechanisms may underlie aspects of neuronal degeneration in these three disorders, some of which may relate to aberrant chromosome 21 expression.

RESUME: Detection de corps de Lewy dans la trisomie 21 (syndrome de Down). La presence de plaques seniles corticales et d’amas neurofibrillaires en quantite suffisante pour justifier un diagnostic neuropathologique de maladie d’Alzheimer est bien etablie chez les individus d’age moyen porteurs de la trisomie 21 (syndrome de Down). Par contre, une relation entre le syndrome de Down et les corps de Lewy, une des manifestations neuropathologiques majeures de la maladie de Parkinson, n’a jamais ete rapportee dans le passe. Dans une etude cliniconeuropathologique de 12 cas de syndrome de Down, des corps de Lewy ont ete retrouves dans la substance noire de deux patients ages respectivement de 50 et 56 ans, qui avaient egalement des manifestations anatomo-pathologiques corticales de type Alzheimer. Aucun de ces cas n’avait de perte neuronale significative au niveau de la substance noire, bien qu’il y eut des pertes neurionales dans le locus coeruleus chez les deux patients. Comme les corps de Lewy de la substance noire sont une manifestation neurohistologique caracteristique de la maladie de Parkinson, leur existence chez des cas de syndrome de Down avec evidence de pathologie de type Alzheimer supporte qu’il y ait un lien etiopathologique entre la maladie de Parkinson, la maladie d’Alzheimer et le syndrome de Down et suggere que des mecanismes pathogeniques communs pourraient etre a la base de certains aspects de la degenerescence neuronale dans ces trois affections, possiblement en relation avec une expression anormale du chromosome 21.


It is well established that most middle-aged individuals with trisomy 21 (Down’s Syndrome) develop neuropathological abnormalities characteristic of Alzheimer’s Disease — cortical senile plaques and neurofibrillary tangle formation — which are usually accompanied by a decline in mental function. Many similarities have been demonstrated between Alzheimer’s Disease and Down’s syndrome from clinical, neuropathological, and neurochemical viewpoints. The finding of a common cerebral amyloid protein (β-A4) in cortical plaques in both conditions, derived from a common precursor molecule (Amyloid Precursor Protein — APP) which maps to chromosome 21, has reinforced an association between these two disorders. Although Lewy body inclusions (accompanied by substantia nigra neuron loss) have been regarded as a hallmark of idiopathic Parkinson’s disease, the recent identification of Lewy bodies in elderly demented individuals showing a pattern of Alzheimer-type pathology distinct from Alzheimer’s disease — characterized by cortical plaque formation and amyloid deposition, but with few or absent neocortical tangles, and only moderate substantia nigra neuron loss — has both enlarged the spectrum of Lewy body disease and emphasized an association between two of the major neurodegenerative diseases — Alzheimer’s and Parkinson’s disease.

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Parkinson’s disease. The possible association between neuro-pathological features of Alzheimer’s and Parkinson’s diseases prompted a neuropathological study to identify Lewy bodies in the brains of middle-aged cases of Down’s syndrome.

MATERIALS AND METHODS

Brains were obtained from 23 individuals with Down’s syndrome over the age of 30 (range 31-74 years) who had died in psychiatric institutions or those for the mentally handicapped in Northumberland. Cases derived from Northgate hospital had been prospectively assessed (CK-N) at regular intervals for evidence of deteriorating mental function and neurological impairment. Control cases (n = 20) were derived from age-matched patients dying in Newcastle General Hospital without any evidence of neurological or psychiatric disease. Table 1 shows the sex and age at death of these two groups. The diagnosis of Down’s syndrome (of the trisomy 21 type) was based on clinical phenotypic features supplemented by confirmatory chromosome studies available in 17 cases. Neuropathological methods followed those established in Newcastle, senile or neuritic plaque density being quantified on frozen von Braunmühl stained sections (25µm) and neurofibrillary tangles being assessed on paraffin tissue blocks taken from standard areas in the four cerebral lobes, limbic cortex, and hippocampus. In paraffin-embedded material, cresyl fast violet (CFV-20µ) and haematoxylin and eosin (H&E-6µ) stains were used for neuronal density measurements and the demonstration of Lewy bodies respectively. Lewy body inclusions were additionally stained immunocytochemically with anti-ubiquitin antisera using peroxidase-antiperoxidase techniques previously described. Limbic and neocortical H&E sections were screened for cortical Lewy body formation, and since Lewy body inclusions in the brain stem preferentially occur in susceptible nuclei, particularly the substantia nigra, locus coeruleus, and dorsal nucleus of vagus, these nuclei were subject to an intensive screening in all brains; sections being obtained from paraffin-embedded tissue blocks taken from upper and lower midbrain levels containing the substantia nigra; from upper and mid-pontine levels containing the locus coeruleus, and from the mid-medulla. Catecholaminergic neuronal densities within the substantia nigra and locus coeruleus were measured by counting the total number of nucleolated neurons in CFV stained sections taken transversely through the brain stem as previously described.

RESULTS

Intracytoplasmic Lewy body inclusions were identified in substantia nigra neurons in two of the 23 cases of Down’s syndrome, aged 50 years (JM) and 56 years (DA) respectively (Figure 1). Both single and multiple Lewy bodies were present within individual neurons in the two cases, the majority of Lewy bodies being in the pigmented neurons of the pars compacta of the substantia nigra, principally in the A9 subgroup but also within smaller neurons constituting the A10 mesolimbic area close to the interpeduncular fossa. In addition cytoplasmic “pale” bodies typical of those associated with Lewy body pathology were also present. Ubiquitin immunoreactivity was positive in the core region of the Lewy bodies. In the cingulate cortex and hippocampal gyrus occasional cortical Lewy bodies were present (below 0.1/cm²), but neocortical (frontal, temporal and parietal lobes) Lewy bodies were only occasionally identified, despite careful screening. Neuronal population densities in the substantia nigra of both individuals were not significantly reduced (87 and 59% of the mean control population respectively in DA and JM); in locus coeruleus and sub-coeruleus neuronal population density was moderately depleted (42 and 52% of the mean control population in DA and JM respectively) although no Lewy bodies were detected in locus coeruleus. In the neo- and archi-cortex, senile plaque density was high in both cases (46.9 and 42.0/mm² respectively, compared with a mean of < 1/mm² in controls) and neocortical tangles were readily identified, supporting a neuropathological diagnosis of Alzheimer’s disease. Clinically evidence of a dementing process was present in these two cases (assessed by CK-N) and both individuals had exhibited considerable deterioration in speech, memory and self-help skills, and behavioural patterns in the 6-12 months prior to death. Neuropathological assessment in these two cases had not revealed extrapyramidal features diagnostic of Parkinson’s disease. No other features of Parkinson’s disease were identified. A third individual aged 62 years was found to have a single Lewy body in the locus coeruleus. No other Lewy bodies were detected in brain stem nuclei in this patient despite an extensive search, nor were high densities of Lewy bodies detected in the cerebral cortex. Alzheimer-type pathology was mild in this case.

### Table 1: Age (at Death) and Sex of 23 Individuals with Down’s Syndrome

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*(LB): Case with Lewy Bodies

Controls: For establishing substantia nigra and locus coeruleus neuronal population density control material was obtained from an extended series of neuropsychiatrically assessed normal cases previously described.
and no associated dementia or extrapyramidal features had been
documented prior to death. Since the presence of Lewy body
pathology in this case was restricted to one neuron within the
locus coeruleus, and could not be confirmed in other neurons or
brain stem nuclei, its significance is uncertain at the present
time and it has not been included as a definitively positive case
in this series.

DISCUSSION

This investigation has shown that one of the major neu-
ropathological features of Parkinson’s disease, neuronal Lewy
body inclusions, occur in a proportion (8.7%) of Down’s syn-
drome cases in middle age. Idiopathic Parkinson’s disease is
characterised neuropathologically by both the presence of Lewy
bodies and neuronal loss in brain stem nuclei, particularly the
substantia nigra. Nigral cell loss was not advanced in Lewy
body-positive cases and nigro-striatal dysfunction had not been
associated with severe extrapyramidal symptomatology in either
case. In both cases with Lewy bodies there was concomitant
neuronal loss in the locus coeruleus, a pattern of brain stem
degeneration which is often seen in cases of idiopathic
Parkinson’s disease and other neurodegenerative disorders.
Although occasional Lewy bodies were identified in the cortex
in both cases the neocortical densities were well below densities
required to warrant a diagnosis of diffuse Lewy body dis-
ease.10 Previous postmortem studies on Down’s syndrome have
documented only mild neuronal loss in the substantia nigra
apparently associated with high densities of neurofibrillary tan-
gles but not Lewy body inclusions.11,12 Neurofibrillary tangles
were present in the substantia nigra neurons in the present study,
but not in the high densities reported previously.12 Future neuro-
chemical studies of striatal dopaminergic activity should clarify
the relationship between nigrostriatal dysfunction and extrapyra-
midal features13 in Down’s syndrome cases.

An increased prevalence of Lewy bodies in Down’s syn-
drome with Alzheimer-type pathology provides further evidence
for a link between the neurodegenerative processes underlying
Alzheimer’s disease and the spectrum of Lewy body disorders.
Immunocytochemical studies of plaques and tangles and Lewy
bodies have demonstrated shared antigens, but there is insuffi-
cient evidence to confirm common pathogenetic mechanisms in
their formation.14,15 Wisniewski et al. recently demonstrated that

Figure 1 — A. Classical Lewy body with a central eosinophilic core and peripheral halo in a pigmented substantia nigra neuron. The Lewy body lies
below the neuronal nucleus with a prominent nucleolus. (Patient DA, 54 years). Magnification ×800. Haematoxylin and eosin (H&E) stain. B. Lewy
body with an eosinophilic core and peripheral halo in a substantia nigra pigmented neuron. An adjacent pale area partially obscured by neuromelanin
pigment represents either a further Lewy body or a pale body — see results section (Patient JM, 52 years). H&E stain, Mag ×900.
an antibody raised against the amyloidogenic protein (gelsolin-variant) in familial amyloidosis of the Finnish type has immunoreactivity to Lewy bodies. The same group subsequently showed that the above antibody had immunoreactivity not only to gelsolin-variant amyloid, but also β-amyloid in a case of Alzheimer’s disease with Lewy bodies.

On current evidence the formation of Lewy bodies in cases of Down’s syndrome is unlikely to be a chance or co-incidental occurrence since the prevalence of “incidental” brain stem Lewy bodies in the 6th decade in the normal population is low (< 1%), particularly when a population has been screened to exclude cases with neurological or psychiatric disease. It remains to be established however, whether Lewy body inclusions in Down’s syndrome represent a primary or direct consequence of the trisomy 21 abnormality, whether they form as a secondary event in brains which are, in an as yet unknown way, susceptible to several neurodegenerative disease processes, or whether they are formed as an epiphenomenon in a small proportion of patients (around 10% for Down’s syndrome on the basis of the current series) with specific neurodegenerative disorders. An involvement of chromosome 21 in some rare familial cases of Alzheimer’s disease has been established by the identification of a missense mutation in the amyloid precursor protein gene (APP 717), which gives rise to a familial dementia syndrome with a range of phenotypic expression but characterized pathologically in the index case by Alzheimer-type pathology and Lewy body formation in the brain stem and cortex. Other connections between Down’s syndrome and Lewy body pathology include the suggestion that the limited nigral degeneration and mild extrapyramidal features in Down’s syndrome may relate to raised levels of the enzyme superoxide dismutase, which is regulated by a gene located on chromosome 21, and has been implicated in the aetiopathology of Parkinson’s disease. The present findings indicate that chromosome 21 abnormalities which give rise to Down’s syndrome may be associated not only with the development of Alzheimer-type pathology in middle age, but also associated, in a proportion of cases, with the development of Lewy bodies.

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REFERENCES