Mosaicism for Trisomy 21 in a Patient With Young-Onset Dementia

A Case Report and Brief Literature Review

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Objective: To describe a case of young-onset Alzheimer disease (AD) due to mosaicism for trisomy 21.

Design: Case report of a single patient.

Setting: Tertiary referral dementia clinic.

Patient: A 55-year-old man with a mild degree of developmental delay but no previous diagnosis of Down syndrome and only minimal physical manifestations of Down syndrome presented with gradually progressive cognitive impairment consistent with probable AD.

Results: Fluorescent in situ hybridization analysis of interphase chromosomes revealed trisomy 21 in 10% of peripheral lymphocytes.

Conclusions: As mosaicism for trisomy 21 can present with no or minimal manifestations of Down syndrome, it may be underdiagnosed as a cause of early-onset AD. Occult mosaicism for trisomy 21 may explain in part the previously described association between family history of Down syndrome and risk of AD. Screening for mosaicism with fluorescent in situ hybridization is indicated in selected patients with mild developmental delay and those with AD of young onset.

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Down syndrome (DS) is caused by trisomy 21 in somatic cells in 95% of cases and more rarely by partial trisomy of portions of chromosome 21.1 Rarer still is demonstrable somatic cell mosaicism for trisomy 21, accounting for 1% to 3% of DS cases.2 The clinical manifestations of mosaicism for trisomy 21 are highly variable, ranging from a fully DS-like presentation3 to an essentially normal phenotype with some persons only being diagnosed after having offspring with full-blown DS.4 These differences are thought to be due to variable numbers of trisomic cells in different tissues. It is possible that a substantial number of cases go undiagnosed; therefore, the true prevalence of this condition in the general population has not, to our knowledge, been established.

By age 50 years, the amyloid plaques and neurofibrillary tangles that characterize the cerebral pathological finding of Alzheimer disease (AD) form in the brains of all persons with DS. This is likely due to the gene for amyloid precursor protein (APP) on chromosome 21 being present in 3 copies.5 A clinical syndrome of progressive dementia occurs, characterized by behavioral regression, memory deficits,6 and deficits attributable to frontal lobe dysfunction.7 In this article, we describe a patient presenting with an acquired dementia consistent with AD who was found to have previously unsuspected mosaicism for trisomy 21 as the likely cause. We then discuss this observation in the context of prior studies suggesting an association of AD and DS in close relatives.
ride and mirtazapine for depression and had been receiving donepezil hydrochloride for 1 year. His wife believed his cognition had improved when treatment with donepezil had been instituted.

He had a history of obstructive sleep apnea and hearing loss attributed to military service and employment in a machine shop. He had attended some special education classes during elementary school and graduated from high school with a C average. He had since been gainfully employed in the Navy and as a welder for 25 years prior to his current job. His father had depression and was forgetful at the time of his death at age 81 years from a gastric ulcer, but otherwise the family history was negative for neurodegenerative or developmental disorders. He had a healthy 17-year-old daughter and 2 brothers aged 54 and 57 years, one of whom was described as having alcoholism. Otherwise, all of his first-degree relatives were healthy without developmental disabilities, learning disorders, or acquired cognitive disorders.

Physical examination revealed a man of normal stature who appeared his stated age. A mild degree of dysmorphism consisting of micrognathia and clinodactyly with a shortened middle phalanx of the fifth digit bilaterally were present (Figure). Many features of DS were notably absent (eg, low-set ears, broad space between the first and second toes, single palmar crease, brachycephaly, oblique eye fissures). His speech was slightly slurred and an eye-closure tic was present. Bilateral sensorineural hearing loss was evident, but otherwise his neurological examination results were within normal limits, including deep tendon reflexes. On bedside cognitive testing, his Mini-Mental State Examination score was 26 of 30 and he scored 21 on the Geriatric Depression Scale, indicating significant dysphoria.

Formal neuropsychological testing was performed, which revealed a Wechsler Adult Intelligence Scale third edition verbal IQ of 85, a performance IQ of 78, and a full-scale IQ of 80, indicating borderline-to-low average intellectual functioning. Estimates of premorbid verbal intellectual abilities, based on performance on the American National Reading Test and the Wechsler Adult Intelligence Scale third edition information subtest, suggested low-average to average abilities. Therefore, the verbal IQ score likely represented a mild decline from his premorbid level of functioning. Neurocognitive testing further confirmed significant deficits in information processing speed (trails A, Stroop word reading), executive function (trails B, Stroop interference), and memory (logical memory 1 and 2, Rey Complex Figure Trial 3-minute recall) with relative preservation of simple attention (forward digit span) and naming. It was felt that neither this degree of learning disability nor his depression fully explained the observed cognitive impairment, in particular the prominent memory deficits.

Results of a prior workup for reversible causes of dementia had been negative. A magnetic resonance image of the brain appeared normal to both the interpreting radiologist and one of us (J.M.R.). A lumbar puncture was performed, which demonstrated normal cell count and total protein levels. Cerebrospinal fluid was sent to Athena Diagnostics (Worcester, Massachusetts), which reported reduced levels of β-amyloid 42 (AB_{42}) (125 pg/mL), elevated total tau levels (334.7 pg/mL), and p-tau levels that were within normal limits (47.45 pg/mL). The interpretation of these findings was that the AB_{42} to total tau ratio was consistent with the diagnosis of AD, although the lack of an elevated p-tau level beyond 61.00 pg/mL decreased the certainty of the specificity of this diagnosis. A clinical diagnosis of probable AD was made. Because of the micrognathia, hearing loss, questionable mild developmental delay, and early-onset dementia, a karyotype was obtained.

Standard karyotype analysis from peripheral white blood cells was performed; of the 60 metaphase cells studied, 1 exhibited trisomy 21. Because of the questionable relevance of this finding, fluorescent in situ hybridization (FISH) testing with DNA probes specific to chromosome 21 was performed on both metaphase and interphase cells. This identified trisomy 21 in 20 of 200 cells (10%) studied.

### COMMENT

The cerebral deposition of β-amyloid in DS has been consistently associated with triplication of the APP gene (GenBank M15333) located on chromosome 21. Essentially all persons with trisomy 21 who live to be 50 years of age have cerebral amyloid plaques and neurofibrillary pathological findings in their brain. A case of DS in which the cerebral pathological finding of AD was absent in the

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**Figure.** The patient with mosaicism for trisomy 21 at ages 6 to 12 months (A), 21 years (B), and 55 years (C). Micrognathia is apparent but many specific features of Down syndrome are absent. D, Clinodactyly with a shortened middle phalanx of the fifth digit bilaterally is present.
brain of a person dying at age 78 years was found to have translocation of part of chromosome 21 in which the locus for the APP gene was not present in 3 copies.15 Furthermore, families with young-onset AD in which the APP gene alone is duplicated on 1 chromosome (3 copies total) have recently been described.16 Elevated plasma levels of Aβ42 and Aβ40, end products of APP metabolism, have been observed in patients with DS27 as well as those with familial AD due to mutations in the gene for APP itself.18 It is now well recognized that decreased levels of Aβ42 and elevated levels of total tau in cerebrospinal fluid are characteristic of AD,19 even in its early stage.20 These changes have also been described in patients with DS with a mean age of 41 years.21 The Aβ42 to total tau ratio in our patient was consistent with these findings. Although cerebrospinal fluid p-tau181 levels were interpreted as being atypical for AD, the ratio of p-tau181 to total tau in cerebrospinal fluid in our patient (0.14) was more like what we have seen in persons inheriting familial AD due to pathogenic presenilin 1 and APP mutations (mean, 0.17) than control subjects (mean, 0.21) using this same assay (J.M.R., Steven G. Younkin, MD, PhD, Domenico Prattico, MD, William Seltzer, PhD, Greg M. Cole, PhD, Daniel H. Geschwind, MD, PhD, Yaneth Rodriguez, PhD, Barbara Saffier, MA, Jeffrey Fein, MA, Sophie Sokolow, PhD, Emily R. Rosario, PhD, Karen H. Glynys, PhD, Arousiak Varpetian, MD, Luis D. Medina, BA, and Jeffrey L. Cummings, MD, unpublished data, November 2007).

Mosaicism for trisomy 21 is thought to most frequently arise from normal fertilization followed by a somatic nondisjunction of chromosome 21 in some cell lines during development.22 We think that the mosaicism found in this 55-year-old man accounts for his progressive cognitive deficits and suggests that the underlying pathology is that of AD. Were there no progressive cognitive impairment, the index of suspicion for trisomy 21 in this individual was low, with the only hints of this diagnosis being a mild degree of learning disability, sensorineural hearing loss, and facial features only weakly suggestive of this entity. We were able to find 3 prior cases of young-onset dementia associated with mosaicism for trisomy 21 in the literature. One was a woman who developed dementia at age 41 years with “no clinical features of DS” but whose daughter had the condition. Routine karyotyping showed that 5 of 50 (10%) of her white blood cells were trisomic for chromosome 21.23 Another was that of a 52-year-old man “living in a staffed hostel” who developed dementia and had results of a single-photon emission computed tomographic scan consistent with the diagnosis of AD (despite some disproportionate involvement of the frontal lobes).24 Another was that of a 45-year-old employed woman with some physical manifestations of DS (brachycephaly, midfacial hypoplasia, clinodactyly, simian crease) who presented with a 2-year history of dementia.25 Head computed tomography showed increased size of the cerebral ventricles, and the glucose metabolic rate was decreased in multiple areas of gray matter, including the parietal regions bilaterally. She was found to have translocation trisomy 21 in 1 of 100 cells in the blood.

It is important to note that in our case, the karyotypic analysis was extended to 60 metaphase cells to identify 1 metaphasic cell trisomic for chromosome 21. Usually no more than 20 cells are analyzed to rule out mosaicism at a 95% confidence level. However, because of the desire to find an explanation for our patient’s young-onset dementia, the more sensitive FISH analyses were performed, which revealed mosaicism for trisomy 21 in 10% of the white blood cells. This raises the possibility that some cases of mosaicism for trisomy 21 may go undetected if FISH is not performed. The true prevalence of this entity in the general population and among those with young-onset AD may therefore be underestimated.

Other associations of DS and AD are not as readily explained by the amyloid hypothesis. Some prior epidemiological studies have found an increased incidence of DS in relatives of persons with AD.26 Heston et al27 found a higher incidence of DS than would be expected by chance in relatives of persons with onset of AD prior to age 65 years. As an excess of only 7 cases in 3044 relatives at risk accounts for this observation, it is possible that occult mosaicism in some index patients might have contributed to this finding, as noted by Hardy et al.28 However, the number of distinct families who showed this relationship (11 families) and the usually distant degree of relationship between the index patient with AD and the patient with DS in this study (only 1 identified person with DS was a first-degree relative) makes it unlikely that this is the entire explanation. Conversely, 1 study29 found a 5-fold higher rate of AD in young mothers of persons with DS. Although the rate of peripheral lymphocyte-defined mosaicism for trisomy 21 in mothers of children with DS is thought to be too low to account for this finding (1.9%-2.4%),30 occult mosaicism in brain, germ cells, and other tissues may be more common. Therefore, undiagnosed mosaicism may at least in part explain the observed association between AD and DS within families.

In this article, we described a 55-year-old man presenting with probable AD who was subsequently diagnosed with mosaicism for trisomy 21 based on FISH analysis of peripheral lymphocytes. Although there was a history of mild developmental delay, he had not previously been suspected of having this diagnosis. As mosaicism for trisomy 21 can present with no or minimal manifestations of DS, it may be underdiagnosed as a cause of young-onset AD. Because such mosaicism may not be diagnosed with routine karyotyping, more widespread use of screening with FISH may be indicated for persons with mild developmental delay and selected cases of young-onset AD. Occult mosaicism for trisomy 21 may in part explain the previously described association between family history of DS and risk of AD.

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REFERENCES