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Alzheimer's Disease and Down's Syndrome: An Overview

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The association between Alzheimer's Disease and Down's Syndrome is well recognized through clinical observations and genetic studies. However, the exact nature and the implications of this link is far from clear as yet. The challenge of diagnosis, genetics and the differences in clinical presentations of Alzheimer's Disease in relation to the Down's Syndrome are reviewed here. Promising areas of research are pointed out and importance of relevant family history is emphasized. A current knowledge in the subject through various studies is presented.

INTRODUCTION

The association between Down's Syndrome [DS] and Alzheimer's Disease [AD] has been well recognized for some time now. Senile plaques were first described in DS brains in 1921 by Struwe. In 1948 Jervis described clinical deterioration and Alzheimer's neuropathology in DS. It is also suggested now that this association is two-sided! On one hand individuals with DS tend to develop AD at some point in their lives if they survive long enough (1–5). On the other hand, there have been some reports of higher than expected frequencies of DS in families with AD (5,6). More recently, a gene defect associated with the "familial Alzheimer's Disease" (FAD) has been mapped to chromosome 21, a chromosome related to DS (7,8). Although some of these findings are disputed, it is worthwhile to review current knowledge in the relationship between these two conditions, while awaiting further information about clinicopathological and genetic association between them.

This overview describes each of these two conditions briefly in relation to the other and then examines the association and the implications of this association between them.

In this overview, the term AD is used to refer to individuals with a provisional diagnosis of Primary Degenerative Dementia of Alzheimer's type.

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Alzheimer's Disease—Diagnostic Accuracy

Primary Degenerative Dementia-Alzheimer's type, is a neuropathological diagnosis. It is the commonest cause of dementia in the general population and is frequently encountered entity in clinical settings in individuals presenting with symptoms of dementia. AD remains mainly a diagnosis of exclusion. Antemortem diagnostic accuracy depends on variety of factors, including patient selection, diagnostic criteria and assessment methods. The postmortem histological verification of the diagnosis is therefore the gold standard (9).

AD in persons with a normal karyotype usually begins with learning and memory deficits, and slowly progresses to involve all the aspects of intellectual activity including judgement, calculation and language (10). In the early stages, psychometric assessment indicates more profound impairment of ideomotor performance than language (10). Dalton et al (11) reported that memory loss, depression and disorientation were the most frequently reported early symptoms of AD in patients with a normal karyotype. In comparison, these are the least frequently reported symptoms in DS individuals who developed AD (11).

There have been several reports systematically describing functional and clinical disturbances in AD in the general population and the reader is advised here to refer to the relevant literature for a detailed description.

The differential diagnosis of dementia has remained a challenge. There are several assessment methods now available which are reasonably sensitive and specific in differentiating causes of dementia. Many investigators have used behavioral observations (12), while the others have used sophisticated neurodiagnostic tools including Computed Tomography (CT), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Xenon inhalation, Electroencephalography (EEG), Evoked potentials and combinations of these for the etiologic diagnosis of dementia (9). However because of factors such as cost/benefit ratio, sensitivity, specificity and accessibility, these methods have remained research tools at large. At present, there is no 'gold standard' criterion or test for the determination of etiology of dementia in clinical settings. The etiologic diagnosis of dementia is critical because some of the other causes are treatable or at least controllable to some extent.

As mentioned earlier, diagnostic accuracy of AD depends on a variety of factors. Tiemay et al (13) reported that accuracy varied between 81% and 88% in clinical settings. A retrospective review by Bolier et al (14) and the report of Joachin et al (15) suggest that elaborate clinical investigations may not enhance diagnostic accuracy. In research settings the diagnostic accuracy may exceed 90% (9). Morris et al (16) reported 100% accuracy in a selected sample of 31 cases with strict inclusion and exclusion criteria without any reference to neuropsychological test performance. These findings apply to the general population with normal or unknown karyotype, where, in absence of a 'gold standard', the selection of a sample is extremely difficult. The issue of diagnostic

accuracy is much more difficult, particularly in the early stage of AD, in the individuals with DS.

Genetics of AD

A genetic basis for some cases of AD was first suggested in 1933 (17). There are case reports describing 'familial Alzheimer's disease' [FAD] (18,19), characterized by early onset dementia. Brietner et al in recent studies (20,21) indicated that the majority of these cases are inherited as an autosomal dominant mutation. In a more recent study (22) they reported a striking increase in cumulative incidence of AD-like illness among the first degree relatives of AD probands. Bird et al (23) noted significant phenotypic heterogeneity in 180 demented individuals from 24 kindreds. They noted clinical and neuropathological differences among families with AD. They raised questions whether there is more than one type of AD, even among FAD patients and whether the phenotypic heterogeneity represents a genetic heterogeneity or is merely an epiphenomenon. St. George Hyslop et al (8) recently reported FAD linked to two chromosome 21q21 loci in four families. One of these two markers is linked to the amyloid B gene. Thus the q21 region of the long arm of chromosome 21 seems to be of particular relevance to AD. Some groups of pedigrees have been assembled in which autopsy determined AD appears to be inherited as an autosomal dominant trait (24). However, the findings of genetic linkage were disputed by Schellenberg et al (24). They found no evidence of linkage between FAD and chromosome 21 markers, including the amyloid B gene. They obtained strong evidence for genetic heterogeneity when they compared their study group to St. George Hyslop et al's group. In this study, most of the evidence for exclusion of genetic linkage came from presenile onset families, although the age of onset was higher than that in St. George Hyslop et al's group. They mentioned the possibility that the gene in chromosome 21 may account only for very early onset FAD.

There also are some other results suggesting genetic involvement in AD. From Heston et al's careful genetic study (3) of 125 families, some relatives of younger probands from autopsy proven AD appear to be at increased risk of Down's syndrome, of myeloproliferative disorders and immune system disorders. Kallmann's (25) investigation of twin pairs suggested monozygotic concordance in AD. All these evidences suggest a genetic component in at least some cases of AD. The exact nature of such genetic contribution is yet to be known.

Down's Syndrome

Ever since the classical description of 'Mongolism' by Langdon Down in 1866, this has remained the most discussed and the most investigated syndrome in the field of mental retardation. The presence of an extra small chromosome was reported by Lejeune in 1959, and was later identified as chromosome 21.

These patients present with a variety of physical characteristics and clinical problems.

Only two decades ago, very few DS individuals survived through mid-adulthood because of associated congenital heart disease, recurrent infections and a variety of other problems. With advancing health care and medical technology, more and more of these individuals survive until 40 years and beyond. According to recent data by Baird and Sadovnick (33), 80% of DS patients without congenital heart disease survive past the age of 30 years. More than 50% of their DS patients reached their 50's and 13.5% reached age 68. These observations are significant in relation to the development of AD neuro-pathology in these individuals.

Studies have shown a higher than average incidence of hypothyroidism (34–37), and at least average incidence, if not higher, of depression (38) in DS. Hypothyroidism in DS is expressed usually as abnormality in one or more thyroid function tests whereas clinically, most of these individuals are asymptomatic. Hollingworth et al (39) compared T4, T3 and TSH levels in 60 DS patients to controls and did not find a significant difference. However, six DS patients had goiter and seven had exophthalmos without goiter. Mani (40) studied 55 adult hospital DS patients; almost all of them were 40 years or over. He found a high frequency of clinical features suggesting hypothyroidism. He recommended screening thyroid function in all DS individuals over 40.

In spite of the lack of evidence pointing to specific causes of hypothyroidism, some have suggested autoimmunity as an etiologic factor for underactivity of the thyroid gland (40). Most of these studies found antibodies to thyroid tissue in DS patients. Increased rates of lymphocytic leukemia and other malignancies and a higher incidence of viral and bacterial infections have also been reported (41–43). A higher incidence of congenital hypothyroidism had also been reported (44).

In 1981, Harrell et al (45) reported beneficial effects of vitamins, minerals and thyroid compound in improving intellectual functioning in persons with DS. They did not evaluate thyroid function prior to therapy. Subsequent attempts to replicate these results with vitamin and mineral therapy were unsuccessful (46). Tiurosh and Toub et al (47), in a double blind cross-over drug-placebo trial, studied a small sample to assess the efficacy of short term thyroid supplement in DS individuals with low borderline thyroid function. They found no significant gains with thyroid supplement. Replication of similar results on a larger sample with more attention towards symptoms of dementia is needed to clarify the indications for thyroid supplement in DS individuals.

A high prevalence of psychiatric disorders in the mentally retarded, including those with DS, has been reported (48). Several case reports of major depression in DS patients have been published (49,50), although there have been some unusual presentations and disagreements in the diagnosis of affective disorders in moderate to severe retardation. Estimates of the prevalence of depression in DS are not available at present. Considering mentally retarded of

all the different etiologies as a single group, it seems likely that affective disorders are at least as common in these individuals as in general population (38). This is particularly significant in DS patient over age of 40, since it complicates the detection of early AD.

Alzheimer's Disease in Down's Syndrome

Alongside the clinical observations and genetic studies in AD patients, there are several reports on DS individuals that suggest a striking association between these two conditions. However, the nature and the clinical and genetic implications of this association remains elusive. Neuropathological changes of AD in brains of DS individuals have been reported for more than 50 years now. Since Struwe's report in 1929, it is well recognized from several studies that virtually all DS individuals 37 years or over develop AD neuropathology, namely, extensive neurofibrillatory degeneration and senile plaques, throughout widespread regions of neocortex (26,27); Certain dermatoglyphic patterns are common in DS patients (28,29,30), and the extension of these studies to their parents showed unusual combinations of dermatoglyphic patterns in parents, particularly in a parent in whom non-disjunction occurred (31). Dermatoglyphic changes similar to DS were also observed in AD by Weinrab who reported a high frequency of ulnar loops on fingertips of both AD and DS patients (32). These and other evidences are becoming clearer as the survival of DS individuals is prolonged.

Clinically, some investigators have observed differences in symptoms of AD in DS patients and in general population. Dalton et al (11) reviewed 35 DS cases from several case reports. They examined 18 descriptive terms of functional and clinical features in these cases excluding language based disturbances. They found that the most frequently reported clinico-functional expression in these cases was clinical seizures (87.8%); followed by personality changes (45.5%) and focal neurological signs (45.5%). The most frequently reported symptoms in patients with AD in general population—i.e. memory loss, depression and disorientation—were the least frequently reported in persons with AD in DS. Besides, differences were noted in self help skills and level of activity in these two groups with AD. Although such comparison between unmatched groups and variable interpretations of retrospective clinical records can provide some direction for further research, it serves little in clarifying the confusion regarding the natural history of AD in DS.

Only one prospective study on AD in DS is reported in literature (51). In this study of 49 clinically demented DS individuals over age 35 followed longitudinally, the average age of dementia onset was 54.2 + 6.1 years, which is much earlier than AD in the general population. In 23 patients who died, the average duration was 4.6 + 3.2 years with no significant difference between the sexes. This study was also able to delineate several features of AD in their DS patients. (i) The first signs of dementia in DS—changes in personality such as

irritability and emotional lability in most cases in their study population—correlate with the late features of AD in general population. (ii) There is a latent period of 2 to 3 decades between the time of onset of neuropathological changes and clinical symptoms. (iii) Prevalence of dementia increases with age. (iv) There is higher incidence of seizures in these individuals as compared to AD patients in general population. (v) Twenty percent of DS outpatients with dementia also developed Parkinson's disease.

DISCUSSION

The available information about the association between AD and DS raises many questions and hypotheses, most of which still remain unanswered. The differences noted in clinical features of AD in DS and in persons with normal karyotype poses a question if there is a different etiology and pathogenesis of AD in these two groups (11). This questions the significance of pathological changes and the clinicopathological correlation in AD. The issue is further complicated by findings of changes identical to AD in many elderly brains in absence of clinical symptoms. Interestingly enough, there are at least two case reports of DS patients—one 49 years and the other 47 years of age—who showed no neuropathology of AD in brain on autopsy (52,53). The prevalence of AD increases with age in DS as well as general population and it is assumed that the aging process begins early and progresses rapidly in DS individuals (54). These observations support Gowers' concept with the implication that AD represents merely a precocious aging of central nervous system (55). If so, one can assume that every individual who lives long enough will develop AD at some point. It may be possible that the symptoms appear only when brain changes are extensive enough or when they involve certain brain areas, such as hippocampus.

However, from epidemiological evidence and clinical observations, there is little doubt that a disease process is involved in AD. Besides the issue of causal factors it also remains to be seen if there are separate factors that control the age of onset in AD.

Almost all DS individuals show AD neuropathology at some point, and up to 85% of these—presumably all if they lived long enough—develop AD (51). Theoretically it seems possible to detect AD in its early phase and to delineate its natural history in this cohort. In that case, the idea of detecting a "herald sign" that predicts or signals the onset of clinical AD appears promising. An individual sign which increases in prevalence with advancing age may need careful scrutiny. Examples of such signs would include primitive reflexes, face-hand test etc., of course, this would require several detailed longitudinal observations.

As mentioned earlier, there are strong indications of a genetic link between AD and DS. Although a chromosomal abnormality in AD needs further confirmation, if present, it could be of tremendous help in screening potential parents with high risk pregnancies. For clinicians, it would be important to include specific questions in obtaining the family history of individuals with these

conditions. In conclusion, there is no doubt about the relationship between AD and DS, but there are several unanswered questions regarding the nature of this relationship. The issues of origin, pathogenesis and the natural history of dementia in DS awaits further prospective studies. The group of DS individuals seems a readily available "ideal" cohort because of their almost certainly known outcome. Obviously, this will be a promising area of research in the field of psychiatry and the study of mental retardation.

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