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Common Versus Uncommon Causes of Dementia

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ABSTRACT

When patients present with a dementia syndrome at a young age, the experienced clinician will automatically include uncommon dementias in the diagnostic considerations, as familial uncommon dementias due to genetic mutations frequently present as early-onset dementias. This paper highlights why uncommon dementias due to genetic mutations, although marginal in terms of prevalence numbers in the total population, are of significance in the quest to unravel the underlying cause of common dementias such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), frontotemporal dementias (FTD) and vascular dementia (VaD).

Introduction

Common versus uncommon: some thoughts about terminology

When acquiring knowledge about dementia, the categories of common and uncommon causes of dementia are soon apparent. Alzheimer's disease (AD) and vascular dementia (VaD) are usually described as the two most common causes of dementia worldwide, with some variation in prevalence between the two depending on ethnic background. Uncommon dementias often appear clinically as part of a syndrome of a complex neurological or systemic disorder and the challenge is to identify them correctly, if possible, because curative treatment might be available in the rare subgroup of reversible dementia syndromes. This

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is often the case in acquired syndromes, such as those due to infections, but also occurs with inherited conditions, such as Wilson's disease.

A common dementia, such as AD (50–60% of all dementia cases), shows similarities with other common diseases, such as type 2 diabetes mellitus or hypertension. These diseases tend to show an increase in incidence and prevalence with age and the underlying disease processes and their causes are often considered to be multifactorial, involving interplay between several genes and environmental factors. Patients with the same disease phenotype can present with a variety of different risk-factor combinations, including different combination sets of predisposing genes. How these various risk factors interact and influence each other's expression remains largely unknown.

As the most frequent types of dementia can be considered complex genetic diseases, it may be surprising that knowledge about the underlying causes of some of the rare causes of dementia, although much less prevalent, is more advanced, especially in monogenic disorders such as Huntington dementia. It is possible, therefore, that we will learn more about the common types of dementia by studying its least frequent causes. In fact, much of what we now know about AD has arisen from the study of its uncommon causes, such as familial AD associated with autosomal dominant inheritance.

Genetic information on rare neurodegenerative dementias applied to common dementias

Familial Alzheimer's disease (FAD)

Familial AD (FAD) is rare, accounting for up to 5% of all cases of AD (Cummings and Cole, 2002). To date, mutations to three genes, the amyloid precursor protein (APP) on chromosome 21, the presenilin 1 (PS1) on chromosome 14, and the presenilin 2 (PS2) on chromosome 1, have been identified as causing FAD with a penetrance of more than 85% (St. George-Hyslop, 2000). All these mutations seem to result in the overproduction of the β-amyloid protein (Aβ), which is generated by cleavage of the APP by the enzymes β- and γ-secretase. The soluble oligomeric form of Aβ is thought to be the major toxic form of Aβ, causing, initiating or contributing to synaptic degeneration and ultimately nerve cell death. The soluble form of Aβ eventually forms fibrils in the extracellular space and is deposited as amyloid plaques, one of the neuropathological hallmarks of familial and sporadic AD. These Aβ fibrils are thought to play a key role in neuroinflammation. This knowledge of Aβ, the development of amyloid plaques and the β-amyloid cascade hypothesis (Hardy and Higgins, 1992), had its origins in the investigation of a very small number of families with FAD. The identification of the relevant genes, as well as their pathogenic mutations, enabled scientists to develop laboratory and animal

models of the illness. In other words, our current understanding of the common sporadic form of AD is heavily based on models generated through the study of rare familial cases of AD. This knowledge should contribute to the development of effective and specific treatments for AD in the near future.

Dementia with Lewy bodies (DLB)

DLB was described systematically in the 1980s as a clinically distinguishable dementia syndrome (Kosaka *et al.*, 1980). Autopsy studies diagnosed DLB in 15–20% of patients with dementia (McKeith, 2002); however, the discrimination from AD pathology is controversial and led to the description of subtypes such as "DLB with senile plaques," "pure DLB" and "plaque-only AD with or without Lewy bodies" (Ince *et al.*, 1998). There is also clinical overlap of symptoms with other dementias such as AD, Parkinson's disease (PD), PD with dementia (PDD) and progressive supranuclear palsy (PSP) (Graeber and Müller, 2003). Thirty-five percent of patients with AD, for example, develop extrapyramidal signs and up to 40% of patients with PD develop cognitive decline (Galvin *et al.*, 2001).

DLB is characterized by visual hallucinations, fluctuations of cognitive function, frequent falls, a sensitivity to the extrapyramidal side-effects of antipsychotic medications, and parkinsonism (McKeith *et al.*, 1996). Like its more common neurodegenerative counterpart AD, DLB is considered to be a "complex disorder" (Graeber and Müller, 2003) and, as is the case for AD, the study of uncommon familial cases of DLB unravels some of its underlying genetic pathological mechanisms.

A few families with an autosomal-dominant inheritance pattern, often with low penetrance, have been described (Brett *et al.*, 2002; Galvin *et al.*, 2002). In a recently described Spanish family with familial DLB, the causative mutation, E46K in the α-synuclein gene on chromosome 4, was identified (Zarranz *et al.*, 2004). This mutation seems to interfere with the normal function of the presynaptic α-synuclein protein. Misfolded α-synuclein is the main component of the Lewy bodies, which in DLB are usually located in the substantia nigra, basal nucleus of Meynert, locus coeruleus and gray matter. Its function is not yet fully understood, but it might be involved in lipid binding and play a role in the regulation of dopamine release at the presynaptic terminal (Galvin *et al.*, 2001). As a result of these investigations, and those of closely related forms of PD, DLB is now described as synucleinopathy, more closely related to PD than to AD pathology.

Frontotemporal dementias or degenerations (FTD)

The third most prevalent form of neurodegenerative dementias following AD and DLB comprises the frontotemporal dementias or degenerations (FTD). This

group includes Pick's disease, FTD without specific neuropathological features, corticobasal degeneration, dementias with parkinsonism linked to chromosome 17 mutations, and dementias associated with motor neuron disease (Lovestone *et al.*, 2002). The various types of FTD have in common a progressive degeneration of the frontal and/or temporal lobes. While FTD are considered less frequent than AD, a lack of epidemiological data, together with confusion regarding diagnostic criteria, results in uncertainty regarding its true prevalence and incidence. FTD typically has its onset before age 65 years. Recent prevalence studies reported a mean age at onset of 52.8 ± 8.7 years in the U.K. and 57.9 ± 9.0 in the Netherlands (Ratnaavalli *et al.*, 2002; Rosso *et al.*, 2003). Prevalence data vary depending on the method and criteria used. A recent study from the province of Zuid-Holland in the Netherlands reported prevalence rates of 3.6, 9.4 and 3.8 per 100 000 at ages 50–59, 60–69 and 70–79 years, respectively (Rosso *et al.*, 2003). A study from the U.K. found a prevalence of 15 cases per 100 000 at age 45–64 years (Ratnaavalli *et al.*, 2002). Compared to AD and DLB, the percentage of familial cases is higher in FTD. Rosso *et al.* (2003) reported in a data set of 345 FTD patients the presence of mutations of the tau gene on chromosome 17 in 32% of patients with other affected first-degree family members, and 43% for all patients with FTD.

Stanford *et al.* (2004) found a tau gene mutation in 25% of patients with familial FTD, but only in 4% of those without a positive family history. The clinical phenotype of tauopathies can vary considerably within the same family (van Swieten *et al.*, 2004). More than 25 different mutations in the tau gene have been reported and a common pathological feature for most of these "mutation-cases" of FTD is the occurrence of fibrillar tau-based pathology in the neurons (Pickering-Brown, 2004). This contributed to the hypothesis that the deposition of tau could be the core pathological process leading to clinical symptoms in tauopathies (Spillantini *et al.*, 1998). However, Stanford *et al.* (2004) recently reported the presence of tau mutations without evidence of accumulation of insoluble tau or tau-based neuronal inclusions. There are also FTD families that show a positive linkage to chromosome 17 without detection of a specific tau mutation and without the typical fibrillar tau pathology of the "mutation-cases."

The implications of uncommon hereditary forms on sporadic forms of vascular dementia

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Strokes represent the pathological basis of VaD. A very small group of VaD cases are due to underlying genetic conditions that increase the risk of strokes. This is a very variable group of conditions including hemoglobinopathies, coagulation

disorders, mitochondrial disorders, connective tissue diseases and angiopathies, among others, which can trigger small- and large-artery disease, embolic or hemorrhagic strokes (Schmidt and Schmidt, 2002).

CADASIL is an uncommon inherited nonamyloid systemic angiopathy caused by mutations in the notch 3 gene on chromosome 19. It has been only recently identified as an uncommon cause of familial VaD, with some 100 families identified worldwide (Dichgans, 2004; Tournier-Lasserve *et al.*, 1993). The clinical phenotype is highly variable, with age at onset as early as the twenties or as late as the seventies, and includes migraine with aura, epileptic seizures, transient ischemic attacks (TIAs), strokes and vascular cognitive impairment and dementia (Chabriat *et al.*, 1995; Dichgans *et al.*, 1998). Age at onset does not correlate with progression or severity of illness and mean age of death is around age 60 years (Desmond *et al.*, 1999). Cognitive impairment is reported in 60% of cases, with two-thirds reaching the clinical threshold of a dementia syndrome at age 65 years. The dementia syndrome is mostly of a subcortical type (Dichgans *et al.*, 1998). But how do mutations in notch 3 cause angiopathy and how does this lead to VaD? The missense mutations lead to a gain or loss of cysteine residues in the extracellular portion of the transmembrane notch 3 protein. The particular part of the protein affected is called the epidermal growth factor (EFG)-like domain (Dichgans, 2004). The angiopathy affects the cerebral small vessels and causes significant damage to the media and endothelium of smooth muscle cells. One hypothesis is that this angiopathy leads to a reduced ability of the blood vessels to autoregulate and thus results in reduced cerebral perfusion (Singhal *et al.*, 2004). The majority of genotype–phenotype correlation studies in CADASIL could not find any impact on the site of the mutation on the phenotype. One possible explanation is that lacunar strokes might develop because of a sudden disruption of perfusion in the blood vessel, which requires, in addition to the genotype, the presence of additional modulating factors to exacerbate the situation (Singhal *et al.*, 2004). One of these environmental factors has been identified as smoking in a recent genotype–phenotype study with 65 families with CADASIL from the U.K. (Singhal *et al.*, 2004). The authors suggested that smoking could adversely affect vasomotor function (Iida *et al.*, 1998) and induce a prothrombotic state (Hioki *et al.*, 2001) in CADASIL patients.

Conclusion

Why are findings of the underlying causes of uncommon dementias relevant beyond the specific rare syndrome? One reason is that they might help us to identify clinically healthy family members at high genetic risk in these rare families with hereditary uncommon dementias. The assessment of these

"carrier" family members prior to clinical diagnosis helps us to understand the temporal relationship of the onset of clinical symptoms, which can also contribute to improving the early diagnosis of common dementias. Geschwind *et al.* (2001) reported that clinically "presymptomatic" carriers of families of familial chromosome 17 FTD showed significant executive dysfunctions decades before expected clinical onset. Findings such as these challenge disease-onset hypotheses and suggest that carriers might be already born with certain altered brain function. If this is true, even the use of the terminology "dementia," defined as acquired cognitive impairment, might need to be reviewed.

Modern drug development research frequently takes its origin from discoveries of pathological mechanisms present in rare-mutation families with AD or FTD with the aim of developing medications that might be of benefit to patients with AD or FTD in general. For example, the recent discovery that inhibitors to the glycogen-synthase kinase-3β (GSK-3β), the enzyme that mediates the phosphorylation of the tau protein, can effectively reduce the phosphorylation of tau (Mudher *et al.*, 2004) might have a significant impact on drug development for treating tauopathies. This discovery is particularly impressive in that one of the substances effectively inhibiting GSK-3β is lithium chloride. Therefore, changes to the underlying hypotheses of pathological processes might also influence future treatment options for the large number of patients with common dementias (Pickering-Brown, 2004).

Conflict of interest

None.

Description of authors' roles

Both authors contributed equally to reviewing the literature and writing the manuscript.

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