Genetic assessment and management of dementia

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Dementia is primarily a phenomenon of later life and, as life expectancy improves, is becoming increasingly important in epidemiological and health economic terms. In general, the common, late-onset disorders causing dementia tend to be multifactorial in aetiology, while early-onset dementia is rare and more likely to follow Mendelian inheritance. The genes responsible for a number of these rare inherited forms have been identified and progress made towards uncovering those genes which influence predisposition to the late-onset forms. This article summarises the main causes of dementia from a genetic viewpoint and highlights some important issues relating to genetic counselling and testing for this group of disorders.

Huntington's disease

Huntington's disease (HD) is a progressive neurodegenerative disorder, characterised by a combination of motor abnormalities, cognitive deficits and neuropsychiatric problems. Inheritance is autosomal dominant, so each child of an affected individual (regardless of gender) has a 50% risk of inheriting the gene. Age at onset varies from early childhood to old age, but most become symptomatic in their fourth or fifth decade. Thus, most affected individuals have completed their families before discovering that they too have the illness. The responsible mutation is a (CAG)n triplet repeat, located in the first exon of the gene which is expanded in affected individuals.[1] The resulting expanded polyglutamine sequence in the huntingtin protein causes the accumulation of intranuclear inclusion bodies (mutant protein fragments) in affected neurones.[2] The age at onset of HD is inversely proportional to the number of repeats.

One unusual aspect of the inheritance of HD is the phenomenon of anticipation when the gene is paternally transmitted. Some of the children of affected fathers have an earlier onset of symptoms because they have inherited a larger expansion than their parent. This instability of the CAG expansion is also seen with repeat lengths towards the upper end of the normal range and is thought to be the basis of new mutations emerging in previously unaffected families.

Diagnosis

The diagnosis of HD is usually based on the characteristic motor abnormalities in an individual with a known family history. The involuntary movements usually begin as abrupt, random movements of short duration (chorea) affecting mainly the distal extremities, but as the disease progresses they tend to become more proximal and increase in duration (dystonia). Together with the involuntary movements, there is progressive slowing and impairment of voluntary movement leading to clumsiness, gait abnormalities, falls, dysarthria and dysphagia.[3] In the later stages there is often severe weight loss, partly due to dysphagia but possibly also to a generalised effect of the abnormal gene product on mitochondrial function. Cognitive changes are characterised by slowing of mental activity, impaired attention and executive dysfunction.[4] The more variable and non-specific neuropsychiatric manifestations include mood disturbances, irritability and aggression, and a severe loss of drive and motivation which progress in tandem with the cognitive changes.[5] The behavioural aspects of the condition are often more distressing and disruptive for patients and carers than either the motor or cognitive manifestations, but fortunately are more amenable to symptomatic treatment.[6]

Genetic testing

It is normal practice to confirm the clinical diagnosis with genetic testing, but it is important to do so only in cases exhibiting motor abnormalities consistent with a diagnosis of HD to avoid the risk of inadvertent predictive testing (see below). Genetic testing can be very useful in isolated cases, for example when the patient

Key Points

- **Dementia in late life is common, usually with a multifactorial aetiology. Early-onset dementia is very rare but much more likely to be Mendelian in origin**
- **Children of someone with the common, late-onset form of Alzheimer's disease (AD) have a risk of developing AD themselves three to four times greater than the general population risk at the same age. However, this is not much more than about 10% at the current average life expectancy**
- **Most of the inherited, early-onset disorders causing dementia follow autosomal dominant inheritance with a 50% risk for children and siblings**
- **Genetic testing is available for Huntington's disease and for a few of the mutations associated with autosomal dominant disorders causing early-onset dementia, but remains a research activity for other forms of dementia**
- **Predictive genetic testing of individuals at risk for Huntington's disease or other inherited dementias should be carried out only in regional genetic centres following accepted genetic counselling protocols**

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was adopted or when both parents died young from other causes. The differential diagnosis of HD includes benign senile chorea, chorea-acanthocytosis, dentorubral pallidoluysian atrophy and some kinds of dominant spinocerebellar ataxia (notably SCA 17).

Predictive testing. All cases of HD have the same genetic cause so testing for the mutation responsible is simple and inexpensive. The delayed onset means that offspring of affected individuals have to live with the knowledge of their 50% risk, imposing a considerable psychological burden given the almost uniquely unpleasant nature of the condition. Some at-risk individuals request genetic testing to discover in advance whether they will be affected (predictive or presymptomatic testing), considering that the certainty of a test result is preferable to continuing at 50% risk, even if the result is unfavourable. There are, however, many potential disadvantages of such a decision, including the psychological effects of an unfavourable result, the emotional impact on the spouse and extended family, and the potential for discrimination in the workplace or difficulty obtaining life insurance.

There is general agreement that predictive testing should be provided only after appropriate genetic counselling, following ethical guidelines drawn up in consultation with the lay organisations.[6] Predictive testing does not appear to be associated with an excess of serious adverse consequences if these guidelines are followed.[7] However, only a minority of those at-risk actually proceed with predictive testing after genetic counselling, most choosing to live with the uncertainty.[8]

Prenatal testing. Genetic testing can also be performed prenatally by direct mutation analysis of fetal DNA (obtained by chorionic villus biopsy) or by prenatal exclusion testing. In the latter, linked genetic markers are used to determine whether a fetus at 25% risk has received from the at-risk parent the chromosome inherited from its affected or unaffected grandparent. Exclusion testing therefore allows the couple concerned either to terminate a pregnancy at 50% risk or to continue a pregnancy at very low risk without simultaneously undertaking a predictive test on the at-risk parent. It has recently become possible to combine both these approaches with *in vitro* fertilisation in the form of pre-implantation genetic diagnosis, removing the need to terminate a high-risk pregnancy.

Alzheimer's disease

The most common cause of dementia is Alzheimer's disease (AD). The prevalence is age-dependent: approximately 3% are affected by age 75, rising to almost 50% in those over 85 years.[9] It is a primary neurodegenerative disorder of the cerebral cortex. The diagnosis rests on the presence of characteristic extracellular deposits of amyloid (plaques) and intracellular neurofibrillary tangles, and can only be made with certainty at autopsy.

Diagnosis

There is no completely reliable laboratory test for AD. In practice, the diagnostic criteria[10] are based on clinical features and neuropsychological tests indicating a dementia syndrome predominantly affecting memory, language, perceptual skills and constructive abilities. There is relative preservation of social skills and personality, at least in the early stages. These clinical features reflect the predominance of neurodegeneration in the parietal and posterior temporal regions. It has recently been suggested that the addition of functional imaging techniques and selected biomarkers might enhance the existing diagnostic criteria.[11]

Genetic mutations

To date, three genes have been associated with autosomal dominant early-onset Alzheimer's disease (EOAD):

1 Missense mutations in the amyloid precursor protein (APP) gene are causative in up to 15% of autosomal dominant families, with duplication of the APP locus on chromosome 21 causing AD with associated cerebral amyloid angiopathy (CAA) in an estimated 8% of families.[12]
2 Patients with trisomy 21 also develop premature AD with CAA in their 40s and 50s due to gene dosage effects.
3 The presenilin 1 (PSEN1) gene[13] on chromosome 14q is associated with particularly early onset and is estimated to account for up to 66% of families manifesting dominant inheritance,[14] while mutations in the PSEN2 gene on chromosome 1 is a rare cause.[15]

Up to 30% of families with EOAD and a pedigree consistent with dominant inheritance do not have a mutation in any of these three genes,[16] suggesting that other loci remain to be discovered. Unlike HD, multiple mutations have been identified in all three of these genes, so predictive testing is possible only where the mutation is already known in the family. Testing is probably clinically justified in the investigation of an affected person only when there is unequivocal early onset and a pedigree suggesting dominant inheritance.

Susceptibility

Familial clustering is also seen with the common, late-onset form (LOAD) due to multiple genes each making a small contribution to susceptibility. The risk of developing LOAD for the offspring of an affected person is three to four times the general population risk at any given age (ie a risk of ca 10% by age 75). Many genes have been implicated as possible susceptibility factors but the only one firmly established to date is apolipoprotein E (ApoE). Relative to the common ε3 allele, possession of an ε4 allele increases the risk of LOAD at any given age, while the ε2 allele is protective.[17] ε4 homozygotes surviving into their ninth decade or beyond have a very high risk of being affected. ApoE genotyping is unsuitable for use as a predictive genetic test because the probability of an ε4/ε4 homozygote developing AD before the average life expectancy is about 40–50%, thus increasing rather than decreasing uncertainty.

Dementia with Lewy bodies

The onset of dementia with Lewy bodies (DLB) is usually in the sixth or seventh decade. It is distinguished clinically from AD by the presence of prominent visual hallucinations, marked fluctuations in cognitive function, sensitivity to neuroleptic medication and associated parkinsonism.[18] Lewy bodies are distributed widely throughout the brain (in contrast to Parkinson's disease (PD) where they are mainly subcortical), often in association with the plaques and tangles of AD. Autosomal dominant inheritance can occur. In some families DLB is caused by mutations in the alpha-synuclein (SNCA) and beta-synuclein (SNCB) genes, both of which are also associated with familial PD. The ε4 allele of ApoE is also thought to increase susceptibility.

Frontotemporal lobar degeneration

Another primary degenerative disorder of the cerebral cortex is frontotemporal lobar degeneration (FTLD). The clinical picture varies depending on the precise anatomical localisation of the neurodegenerative changes, but the predominant features are personality and behavioural changes (apathy or disinhibition), with impaired executive function and language. Three broad clinical presentations are recognised:

- frontotemporal dementia
- progressive aphasia, characterised by impaired speech production without loss of comprehension, and
- semantic dementia, where the meaning of words and ability to name objects is lost.[19]

Depending on the nature of associated neuronal inclusions, cases may be categorised as:

- ubiquitin-positive
- tau-positive (Pick bodies), or
- lacking distinctive histology.

This classification does not correspond clearly to distinct clinical presentations. Ubiquitin-positive cases are sometimes associated with motor neurone disease, while parkinsonism may be a feature of those with tau pathology.

Genetic mutations

Up to 60% of patients with FTLD have a positive family history, usually consistent with autosomal dominant inheritance.[20] Two genes on chromosome 17 account for many of these dominantly inherited families. Tau-positive cases are associated with missense or splice site mutations in the gene encoding microtubule-associated protein tau,[21] while families with the ubiquitin-positive form have mutations in the progranulin gene.[22] Two other genes on chromosome 3 and 9 account for a small number of additional families.

CADASIL

The onset of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is usually in the third decade, with complete penetrance by the age of 40. Clinical features may include migraines, neuropsychiatric manifestations, seizures, recurrent strokes, progressive dementia, gait abnormalities and pseudobulbar palsy. Characteristic changes are seen in the anterior frontal and temporal lobes and in subcortical structures on magnetic resonance imaging. CADASIL is caused by mutations in the NOTCH3 gene on chromosome 19.[23]

Conclusions

Other causes of dementia than those discussed above include the prion diseases, PD, and multi-infarct dementia, all of which are subject to some degree of genetic susceptibility. Diagnosis is crucial for accurate genetic counselling, but the vast majority of those seeking genetic counselling for a family history of dementia face the relatively reassuring risks associated with multifactorial rather than single-gene inheritance.

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Acute presentations of inherited metabolic disease in adulthood

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It has been over a century since Sir Archibald Garrod first recognised the existence of inherited metabolic diseases (IMD).[1] Technological and scientific advances have gradually led to greatly increased understanding of their aetiology and pathogenesis, and have ultimately resulted in effective therapies. Treatment has dramatically altered the natural history of metabolic disorders. Examples include:

- the phenylalanine-restricted diet for phenylketonuria[2]
- uncooked cornstarch for the hepatic glycogenoses[3]
- cobalamin for vitamin B12-responsive methylmalonic acid[4]
- nitisinone for tyrosinaemia type 1[5]
- enzyme replacement therapy for Gaucher disease.[6]

Not only can more than ever before be done today for patients but, as laboratory technology improves, more individuals with IMD are being diagnosed. Thin layer chromatography, high-peformance liquid chromatography, gas chromatography-mass spectrometry and tandem mass spectrometry (TMS) have successively led to easier screening (both primary and secondary), making diagnoses that were previously missed.

Paediatric metabolic medicine has achieved its aims:

- to prevent untreatable disease with genetic counselling and antenatal testing
- the provision of effective therapy to children with IMDs so that they can survive childhood and integrate into society.

Affected individuals can also present for the first time in adulthood. It is important for clinicians working in the adult sector to be aware of these disorders, not only to manage survivors of childhood but also to recognise patients presenting in adulthood. This article describes some acute clinical scenarios in which IMDs need to be considered. As they are genetic diseases, missing the diagnosis may have implications both for the affected individuals and for their families.

Encephalopathy/coma

IMD is high in the differential diagnosis when infants present with encephalopathy, but in adult medicine the emphasis tends to be on acquired conditions such as infection or poisoning. Even though most patients will have blood glucose and arterial blood gas measured, hypoglycaemia and acidosis are often (and often rightly) thought to be secondary features and are treated but not investigated further. It is important to remember that in the unconscious patient metabolic disturbance can sometimes be the primary cause.

In any patient with metabolic acidosis, it is important to calculate the anion gap. A raised anion gap suggests the presence of an abnormal metabolite and needs further investigation. Measuring plasma lactate or detecting urinary ketones by dipstick will often be helpful. Plasma ammonia concentrations should be readily available in all acute settings but are rarely measured on the adult intensive therapy unit. They should form part of the assessment of any unconscious