Cerebral Autosomal Dominant Arteriopathy

Epidemiology

This is a rare familial form of multi-infarct dementia and other neurological problems due to a defect of NOTCH3 gene on chromosome 19. There are probably several slightly different but close mutations. It is inherited as autosomal dominant, and there are familial clusters. The mutation is in the NOTCH3 gene. There is no difference in incidence between the sexes. Worldwide about 400 affected families have been reported.

The true prevalence of CADASIL is unknown, but a Scottish study suggested the prevalence of CADASIL in that population was about 2 in 100,000 adults.

Risk factors

Usually a parent is affected. New mutations are rare and penetrance is high. Children of affected parents have a 50% chance of inheriting the disorder.

Serious hereditary diseases are rarely autosomal dominants as they tend to be self destructive by killing the affected person before he or she can reproduce. However, in CADASIL (as in Huntington's chorea) the disease does not usually strike until after the individual has had a family. Genetic counselling is very important, aided if possible by predictive testing.

Presentation

There are no generally accepted diagnostic criteria but features that may suggest the disease include:

- Stroke-like episodes before age 60 years
- Cognitive disturbance (dysexecutive syndrome)
- Behavioural abnormalities
- Migraine with aura
- Family history suggesting an autosomal dominant inheritance is usual but not essential

Not everyone presents with all features but the following gives an indication of presentation and chance of occurrence, although the figures are based on different series. Findings vary between families and there may be other genetic modifiers:

- CADASIL starts with migraine with aura during the 3rd decade in 30 to 40% of patients. It is followed by ischaemic events between the 30s and 60s, and progressing to dementia and death.
- Death is often during the 6th decade. Most of the recurrent strokes, or transient ischaemic attacks (TIAs), are classical lacunar infarcts (LACIs). They are not related to hypertension or any other vascular risk factors.
Subcortical ischaemic events occur in 84% with progressive or stepwise subcortical dementia and pseudobulbar palsy in 31%.[8]
- Migraine with aura occurs in 22% and mood disorders with severe depressive episodes in 20%.
- In one series there was progressive dementia, gait abnormalities, and, in some, symptoms suggestive of Parkinson's disease.[9]
- In another series[10] the most consistent finding was ischaemic episodes, usually classical TIAs or lacunar strokes, but occasionally insidious deficits that developed over several days. Cognitive deficits were seen in 59%, migraine in 38%, psychiatric symptoms in 30% and epilepsy in 10%.
- Dementia may start as early as age 35 and, by age 45, over 50% have features of dementia.[11]

Clinical suspicion
The disease is probably underdiagnosed. The diagnosis should be considered not only in patients with recurrent small subcortical infarcts leading to dementia, but also in the patients with TIAs, migraine with aura and mood disturbances, whenever MRI scanning reveals prominent signal abnormalities in the subcortical white matter and basal ganglia.

Differential diagnosis
- Multiple sclerosis - MRI scanning is important to differentiate[12]
- Binswanger's disease (subcortical vascular dementia)[13]
- Primary angiitis of the nervous system
- Vascular dementia (other forms)

Investigations
- MRI scans show infarcts within the deep white matter. They are found in the anterior temporal lobe with great specificity and sensitivity. The external capsule is less often involved.
- CADASIL may be diagnosed on the basis of characteristic hyperintensities in T2-weighted MRIs.[14] Multiple LACIs located mainly in the basal ganglia and frontal white matter lead to a cognitive decline and finally to dementia. Subtle MRI changes may be seen as early as age 21 and before clinical features.
- The diagnostic pathology of CADASIL is a non-amyloid, non-atherosclerotic microangiopathy. It affects the leptomeningeal and perforating arteries of the brain - the media of these vessels is thickened by eosinophilic periodic acid-Schiff-positive granular deposits. On electron microscopy, this material corresponds to osmiophilic immunoglobulin-like deposits located in close proximity to vascular smooth muscle. The clinical features are neurological but the arteriopathy is generalised and so brain biopsies are not required. Testing can be done on biopsies of skin.[14]

Molecular genetic testing can be used for:
- Confirming the diagnosis
- Predictive testing of a potential carrier who has not yet developed features of the disease
- Prenatal diagnosis

The mutation detection rate is said to be in excess of 95%.

Associated diseases
A Dutch study found that nearly 25% had a history of myocardial infarction.[15]

Management
Management is purely supportive as no effective treatment exists. The possible benefit of low-dose aspirin is unproven. Acetylcholinesterase inhibitors (eg donepezil) have no significant effect on cognitive function although may have some benefit on executive function.[16] More research is needed.

Prognosis
Mean age at death was 53.2 ±10.9 years for males and 59.3 ± 8.8 years for females.[10]

Prevention

Prenatal testing is possible. The ethics of testing young people for a disease that does not normally present until later life suggests that it is best left until after age 18. Fetal testing from amniocentesis or chorionic villus sampling is feasible.

Further reading & references

- Gene reviews; CADASIL
- Genetics Home Reference; CADASIL

2. Cerebral Arteriopathy; CADASIL Online Mendelian Inheritance on Man (OMIM)
3. Genetics Home Reference; CADASIL
13. Binswanger's Disease; National Institute of Neurological Disorders and Stroke

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