Adrenoleukodystrophy (ALD) and Adrenomyeloneuropathy (AMN)

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Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) are important potential underlying diseases to consider in boys and men with idiopathic (unexplained) adrenal failure/Addison's disease where adrenal antibodies cannot be detected and there is no other obvious cause of adrenal failure.

In ALD/AMN the adrenal failure is most commonly detected during childhood or adolescence. Studies indicate that the proportion of cases in which Addison's disease is attributable to ALD is age dependent. It is highest when the adrenal insufficiency manifests before 15 years, where it appears to be responsible for one third of cases of primary adrenal failure in males.[1]

The frequency of ALD/AMN in men with Addison's disease is not clear, and smaller, localised studies may have been influenced by the tendency for clusters to develop where there is an affected family. Larger, more recent studies have tended to find lower rates of ALD/AMN among both boys and men.

A large-scale Norwegian study, covering 75% of all known male cases of Addison's in Norway, found that X-linked adrenoleukodystrophy was responsible for 1.5% of all adult male cases, and for 15% of those primary adrenal cases of non-autoimmune cause.[2] Similarly, doctors in Portugal[3] found no instances of ALD/AMN in 22 men with adrenal failure.

However, many medical papers describe one or more males in whom adrenal failure developed during adulthood. As two examples:

1. Dr Kong and her colleagues published a retrospective study from the Nottingham area in 1994 looking at all patients diagnosed with Addison's disease between 1987 and 1993.[4] During that time 63 females and 23 males were diagnosed and 3 of these males (13%) from unrelated families turned out to have ALD/AMN as the cause of their adrenal gland failure.
2. Dr Laureti and colleagues in Italy found ALD/AMN in two of the nine men (22%) whose adrenal failure was diagnosed in adulthood in their area.[5]

In both studies the diagnosis of Addison's disease had been made well into adult life – at the ages of 32, 33, 35, 36 and 53.

This emphasises the importance of considering underlying ALD/AMN in any male with unexplained antibody negative Addison's disease, especially those who develop adrenal problems before the age of 40. The diagnosis can be excluded by a widely available blood test – measurement of very long chain fatty acids (VLCFA) in the blood. This test currently costs less than £100 to perform in the UK.

Making the diagnosis early can be very important. It may prevent unnecessary medical tests if symptoms of ALD/AMN develop at a later stage. In the future it could mean that individuals with ALD/AMN who present initially with adrenal failure might have treatment options available to prevent later onset of neurological disease. It may also help to identify other affected males or females with the disease in the wider family.

ALD/AMN are conditions caused by unusual genetic mutations that are passed down within families. A family medical tree, listing known long-term conditions such as heart disease, rheumatoid arthritis, asthma, thyroid disease or diabetes, as well as cause of death where known, can be helpful. If there is a family history of ALD/AMN, there may be suggestions of premature death, possibly associated with multiple sclerosis or other suspected neurological/psychiatric conditions, among the grandparents, uncles, aunts or cousins.

To quote Dr Kong from an article in the Lancet in 2008 where she and her colleagues described another man whose adrenal failure was identified at 32 years of age:

"ALD should be borne in mind as a differential diagnosis in men with isolated multiple sclerosis and in men with Addison's disease who are antibody-negative."

To quote Dr Horn from the 2013 survey of the Norwegian Addison's registry:

"We found X-linked adrenoleukodystrophy to be an uncommon cause of Addison's disease in adult men. However, this aetiological diagnosis has far-reaching consequences both for the patient and for his extended family. We therefore recommend that all adult men with nonautoimmune Addison's disease be analysed for levels of very long-chain fatty acids (VLCFA)."

If you think that testing might be appropriate for you, we recommend that you discuss this with the endocrinology doctor(s) looking after you.

References

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