LETTER TO THE EDITOR

Age-dependent penetrance among females with X-linked adrenoleukodystrophy

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Sir,

In an interesting study recently published in Brain, Engelen et al. (2014) describe a cohort of 46 Dutch heterozygotes with X-linked adrenoleukodystrophy, representing 26 kindreds. They found that signs and symptoms of neurological involvement increased with age among the females included. However, the authors express concern that selection bias may have skewed their results towards preferential inclusion of symptomatic subjects.

We reported the same phenomenon of age-dependent penetrance among females in our own study (Horn et al., 2013), published in Pediatric Neurology (March, 2013), but not referred to in the present article. This was the first prevalence study that looked at males and females with X-linked adrenoleukodystrophy using modern diagnostic methods, including 26 adult females belonging to 13 separate kindreds. This study had no selection bias, as all known cases of X-linked adrenoleukodystrophy in Norway (population 5 million) were included. All symptomatic females were older than 50 years, the asymptomatic ones were younger than 50 years. Asymptomatic females with neurological signs of long tract involvement constituted a middle group age-wise. Four females, reportedly healthy, were unavailable for clinical examination. Naturally, asymptomatic females with no symptomatic family members could not be included except by screening measures, not yet established in Norway.

The findings by Engelen and coworkers lend support to our own results. Subsequently, further support was found in our recent study (Horn et al., 2014) of small nerve fibre involvement in subjects with a disease-causing mutation in the ABCD1 gene (males and females with or without symptoms of X-linked adrenoleukodystrophy): 10 of 11 subjects showed evidence of small nerve fibre involvement. This was found even among young, asymptomatic heterozygotes with no clinical signs of emerging myelopathy, and increased with age and severity of symptoms. This indicates that the central and peripheral nervous system is affected in most or all heterozygotes with a mutation in the ABCD1 gene, hence these subjects are not simply carriers of a gene mutation.

References