Cognitive impairment in SPG4 AD-HSP: the Irish experience.

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The division of hereditary spastic paraparesis (HSP) into "pure" and "complicated" forms may be artificial. Mutations in *SPAST* (SPG4 locus), responsible for about 40% of the AD-HSP cases, cause a predominantly pure HSP but there is evidence that SPAST mutations may cause a complicated phenotype.

We have, in a series of papers in the last 13 years, described progressive cognitive impairment and dementia in five families with SPG4-linked ADHSP due to *SPAST* mutations {Webb and Hutchinson, 1998; Webb et al., 1998; Byrne et al., 2000; McMonagle et al., 2004; Murphy et al., 2009}. Cognitive impairment was found only in AD-HSP families with *SPAST* mutations and not in families where the *SPAST* mutation had been excluded {McMonagle, 2000}. The index case of one family had evidence of progressive cognitive decline and dementia; she died and post-mortem features were described {Murphy et al., 2009}.

The relationship between cognitive impairment and ADHSP remains controversial. While other researchers have also described cognitive impairment in families with SPG4-linked HSP, some have suggested that apparent cognitive decline may be representative of a constitutionally low IQ and others argue that cognitive impairment, when it occurs, is mild and subclinical and not an intrinsic feature of SPG-4 linked HSP.

Further work has been suggested. We aim to examine cognition in all older members of our families with SPAST mutations to determine the prevalence of cognitive impairment and dementia. A collaborative study with other groups interested in this question would be worthwhile.