Hereditary Spastic Paraplegias: phenotype and disease course in a cohort of 600 cases

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Hereditary spastic paraplegias (HSP) are genetically driven disorders with the hallmark of progressive spastic gait disturbance. To investigate the phenotypic spectrum, progression rates, prognostic factors and genotype specific differences we analyzed baseline data of a continuous, prospective cohort.

We recruited 608 HSP cases from 519 families of mostly German origin. Clinical severity was assessed by the Spastic Paraplegia Rating Scale (SPRS). Complicating symptoms were recorded by a standardized inventory.

Family history indicated autosomal dominant (49%), recessive (12%) and sporadic disease (39%). We observed a male predominance especially in sporadic cases. SPG4 was by far the most common genotype and was four times as common as SPG3 even in early onset cases. Major variability in age at onset and complicating symptoms were observed within all genotypes. Mean progression rate was 0.95 SPRS points per year in patients with disease duration >10 years with dependence on the underlying genotype. Later disease onset, complicating features like peripheral motor involvement and the SPG11 genotype were associated with faster disease progression. Even after a disease duration of 40 years, less than one third of patients depended on a wheelchair with an even lower frequency in early-onset cases.

This cross-sectional cohort study provides first large-scale data on disease manifestation, progression and modifying factors with relevance for counselling of HSP families. Future interventional studies will require stratification for modifiers of disease progression identified in this study. Prospective longitudinal studies are on the way to verify progression rates calculated in this baseline analysis.