Diagnostic flowchart for Hereditary Spastic Paraplegias (HSP)

suggestions for comprehensive phenotyping in HSP

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ERN-RND is a European Reference Network established and approved by the European Union. ERN-RND is a healthcare infrastructure which focuses on rare neurological diseases (RND). The three main pillars of ERN-RND are (i) network of experts and expertise centres, (ii) generation, pooling and dissemination of RND knowledge, and (iii) implementation of e-health to allow the expertise to travel instead of patients and families.

ERN-RND unites 32 of Europe's leading expert centres in 13 Member States and includes highly active patient organizations. Centres are located in Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Slovenia, Spain and the UK.

The following disease groups are covered by ERN-RND:

- Ataxias and Hereditary Spastic Paraplegias
- Atypical Parkinsonism and genetic Parkinson's disease
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Ion Accumulation
- Frontotemporal Dementia
- Huntingtons' Disease and other Choreas
- Leukodystrophies

Specific information about the network, the expert centres and the diseases covered can be found at the networks web site www.ern-rnd.eu.

Recommendation for clinical use:

The European Reference Network for Rare Neurological Diseases developed the Diagnostic Flowchart for HSP to help guide the diagnosis. The Reference Network recommends the use of this Diagnostic Flowchart.

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METHODOLOGY

The development of the Diagnostic Flowchart was done by the Disease group for Ataxia and Hereditary Spastic Paraplegias of ERN-RND.

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Flowchart development process:

- Development of flowchart – June – November 2017
- Discussion/Revision in ERN-RND disease group – November 2017 – June 2018
- Consent on diagnostic flowchart during ERN-RND annual meeting 2018 – 08/06/2018
- Consent on document by whole disease group – 15/11/2018

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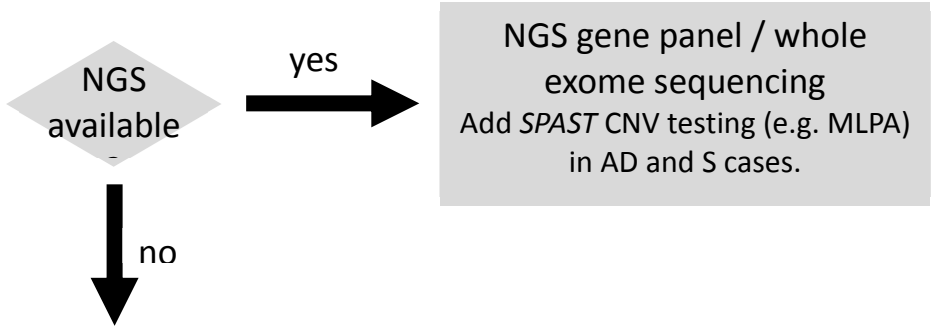
Diagnostic flowchart for HSP

Genetic testing strategy



HSPs are phenotypically highly variable and genetically highly heterogeneous. Single gene testing other than indicated below is therefore not recommended. Instead, comprehensive NGS-based gene panels or whole exome/genome sequencing should be employed as a first line diagnostic testing.

Exclusion of secondary causes (structural, inflammatory, metabolic) and diagnostic biomarkers

MRI brain and spinal cord
CSF (*consider*): white cell count, oligoclonal bands
Lab parameters (*consider, non-exhaustive*):

- Acylcarnitine profile and carnitine (lipid metabolism disorders)
- Ammonia (hyperarginemia and HHH),
- Arylsulfatase A (metachromatic leukodystrophy),
- Biotinidase activity (biotinidase deficiency),
- Cholestanol/urinary bile alcohols (cerebrotendinous xanthomatosis)
- Cholestanoic acid, phytanic acid, pristanic acid, pipecolic acid, docosahexaenoic acid, plasmalogens (peroxysomal disorders),
- Copper/coeruloplasmin/zinc/(24h copper and zinc excretion in urine) (copper deficiency),
- Folic acid (folate deficiency),
- Galactosylceramidase (Krabbe disease),
- HTLV-1 (tropical spastic paraparesis), HIV (HIV myelopathy),
- 25-/27-Hydroxycholsterol (SPG5,
- Lactate, pyruvate (mitochondrial disorders, disorders of gluconeogenesis/pyruvate metabolism and others)
- Plasma amino acids (disorders of amino acid metabolism),
- Treponema pallidum (neuroborreliosis),
- Urine organic acids (organic acidurias),
- VDRL/RPR (neurolues),
- Very long chain fatty acids (adrenoleukodystrophy/ adrenomyeloneuropathy, peroxystomal disorders),
- Vitamine B12/homocysteine/methylmalonic acid (vitamine B12 deficiency),
- Vitamine E (vitamine E deficiency),

Other tests (*consider*):

- Optical Coherence Tomography (ARSACS), electroretinography, EMG, evoked potentials

History of toxic exposure: nitrous oxide, heroin, cassava root (Konzo), grass pea (neurolathyrism), radiation, clioquinol, organophosphates, intrathecal or intravenous chemotherapy (e.g. methotrexate, cytarabine, cisplatin, cladribine, carmustine, TNF antagonists), portosystemic shunting in liver cirrhosis (hepatic myelopathy)

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European Reference Networks

https://ec.europa.eu/health/ern_en

European Reference Network
for rare or low prevalence complex diseases

Network
Neurological Diseases
(ERN-RND)

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