Diagnostic flowchart for Hereditary Spastic Paraplegias (HSP)

suggestions for comprehensive phenotyping in HSP

Published by ERN-RND: 11th February 2019

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

Introduction to the European Reference Network for Rare Neurological Diseases (ERN-RND):

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.

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

Disclaimer:

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published, endorsed or affirmed by ERN-RND are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new information may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgement of the treating provider, as the information does account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ERN-RND provided this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. ERN-RND specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ERN-RND assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

METHODOLOGY

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

Disease group for Ataxia and Hereditary Spastic Paraplegias:

Disease group coordinators:

Caterina Mariotti[16;] Rebecca Schuele-Freyer[14]

Disease group members:

Healthcare professionals:

Segolene Ayme[1]; Enrico Bertini[2]; Kristl Claeys[3]; Maria Teresa Dotti[4]; Alexandra Durr[1]; Antonio Federico[4]; Josep Gámez[5]; Paola Giunti[6]; David Gómez-Andrés[5]; Kinga Hadziev[7]; York Hellenbroich[8]; Jaroslav Jerabek[9]; Jiri Klempir[11]; Thomas Klockgether[12]; Thomas Klopstock[13]; Norbert Kovacs[7]; Ingeborg Krägeloh-Mann[14]; Berry Kremer[15]; Alfons Macaya[5]; Bela Melegh[7]; Maria Judit Molnar[8]; Isabella Moroni[16]; Alexander Münchau[8]; Esteban Muñoz[17]; Lorenzo Nanetti[16]; Andrés Nascimento[17]; Mar O'Callaghan[17]; Damjan Osredkar[18]; Massimo

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

Pandolfo[19]; Joanna Pera[20]; Borut Peterlin[18]; Maria Salvadó[5]; Ludger Schöls[14]; Deborah Sival[15]; Matthis Synofzik[14]; Franco Taroni[16]; Sinem Tunc[8]; Bart van de Warrenburg[21]; Judith van Gaalen[21]; Martin Vyhnálek[9]; Michèl Willemsen[21]; Ginevra Zanni[2]; Judith Zima[7]; Alena Zumrová[9]

Patient representatives:

Lori Renna Linton[10], Mary Kearney[10], Cathalijne van Doorne[10]

[1] Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salepétrière, France: Reference Centre for Rare Diseases 'Neurogenetics'; [2] Pediatric hospital Bambino Gesù, Rome, Italy; [3] University Hospitals Leuven, Belgium; [4] AOU Siena, Italy; [5] Hospital Universitari Vall d'Hebron, Spain; [6] University College London Hospitals NHS Foundation Trust, United Kingdom; [7] University of Pécs, Hungary; [8] Semmelweis University, Hungary;[8] Universitätsklinikum Schleswig-Holstein, Germany; [9] Motol University Hospital, Czech Republic; [10] Patient representative; [11] General University Hospital in Prague, Czech Republic; [12] Universitätsklinikum Bonn, Germany; [13] Klinikum der Universität München, Germany; [14] Universitätsklinikum Tübingen, Germany; [15] University Medical Center Groningen, Netherlands; [16] Foundation IRCCS neurological institute Carlo Besta – Milan, Italy; [17] Hospital Clínic i Provincial de Barcelona y Hospital de Sant Joan de Déu, Spain; [18] University Medical Centre Ljubljana, Slovenia; [19] Université libre de Bruxelles, Belgium; [20] University Hospital in Krakow, Poland; [21] Stichting Katholieke Universiteit, doing business as Radboud University Medical Center Nijmegen, Netherlands.

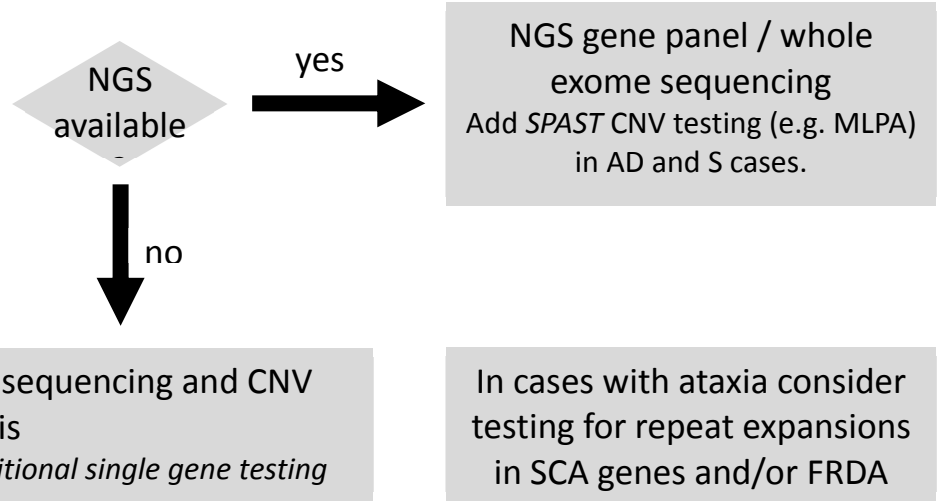
Flowchart development process:

- 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

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

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)

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).