DIAGNOSTIC FLOWCHART FOR EARLY-ONSET ATAXIAS

EUROPEAN REFERENCE NETWORKS
FOR RARE, LOW PREVALENCE AND COMPLEX DISEASES

Share. Care. Cure.

Consented by ERN-RND: July 2020
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 as well as 10 affiliated partners in 20 member states and includes highly active patient organizations. Centres are located in Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, 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
- Huntington’s Disease and other Chorea
- Leukodystrophies

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

Recommendation for clinical use:
The European Reference Network for Rare Neurological Diseases developed the Diagnostic Flowchart for early-onset Ataxias to help guide the diagnosis. The Reference Network recommends the use of this Diagnostic Flowchart.

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 not 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.
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:**

Enrico Bertini\(^1\), Alfons Macaya\(^9\), Caterina Mariotti\(^6\), Rebecca Schuele-Freyer\(^18\)

**Disease group members:**

Anne Torvin Møller\(^1\), Maria Teresa Dotti\(^2\), Antonio Federico\(^2\), Alexandra Durr\(^3\), Michael Freilinger\(^4\), Sandy Siegert\(^4\), Sylvia Boesch\(^5\), Wolfgang Nachbauer\(^5\), Isabella Moroni\(^6\), Lorenzo Nanetti\(^6\), Franco Taroni\(^6\), Jiri Klemper\(^7\), Esteban Muñoz\(^8\), Mar O’Callaghan\(^8\), Andrés Nascimento\(^8\), Alejandra Darling\(^8\), Carlos Ortez\(^8\), Josep Gámez\(^9\), Maria Salvador\(^9\), David Gómez-Andrés\(^9\), Thomas Klopstock\(^10\), Susanne Schneider\(^10\), Martin Vyhnálek\(^11\), Alena Zmurová\(^11\), Jaroslav Jerabek\(^11\), Klara Hruba\(^11\), Ginevra Zanni\(^12\), Maurizio Petrarca\(^12\), Gessica Vasco\(^12\), Francesco Nicita\(^12\), Maria Judit Molnar\(^13\), Bart van de Warrenburg\(^14\), Michèl Willemsen\(^14\), Judith van Gaalen\(^14\), Charlotte Haaxma\(^14\), Margit Lili\(^15\), Thomas Klockgether\(^16\), York Hellenbroich\(^17\), Alexander Münchau\(^17\), Sinem Tunc\(^17\), Martje Pauly\(^17\), Rebecca Herzog\(^17\), Ludger Schölz\(^18\), Ingeborg Krägeloh-Mann\(^18\), Matthis Synofzik\(^18\), Peter Martus\(^18\), Massimo Pandolfo\(^19\), Paola Giunti\(^20\), Julie Vallortigara\(^20\), Fran Borovecki\(^21\), Joanna Pera\(^22\), Kristl Claeys\(^23\), Berry Kremer\(^24\), Deborah Sival\(^24\), Borut Peterlin\(^25\), Damjan Osredkar\(^25\), David Neubauer\(^25\), Norbert Kovacs\(^26\), Bela Melegh\(^26\), Kinga Hadziev\(^26\), Judith Zima\(^26\), Mary Kearney\(^27\), Lori Renna Linton\(^27\)

\(^1\)Aarhus Universitetshospital, \(^2\)AOU Siena, Italy, \(^3\)Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, France: Reference Centre for Rare Diseases ‘Neurogenetics’, \(^4\)Center for Pediatric Rare Neurological Diseases / Dept. of Pediatrics, Medical University of Vienna, \(^5\)Center for Rare Movement Disorders / Dept. of Neurology, Medical University Innsbruck, \(^6\)Foundation IRCCS neurological institute Carlo Besta – Milan, Italy, \(^7\)General University Hospital in Prague, Czech Republic, \(^8\)Hospital Clinic i Provincial de Barcelona y Hospital de Sant Joan de Déu, Spain, \(^9\)Hospital Universitari Vall d’Hebron, Spain, \(^10\)Klinikum der Universität München, Germany, \(^11\)Motol University Hospital, Czech Republic, \(^12\)pediatric hospital Bambino Gesù, Rome, Italy, \(^13\)Semmelweis University, Hungary, \(^14\)Stichting Katholieke Universiteit, doing business as Radboud University Medical Center Nijmegen, Netherlands, \(^15\)Tartu University Hospital, Estonia, \(^16\)Universitätsklinikum Bonn, Germany, \(^17\)Universitätsklinikum Schleswig-Holstein, Germany, \(^18\)Universitätsklinikum Tübingen, Germany, \(^19\)Université libre de Bruxelles, Belgium, \(^20\)University College London Hospitals NHS Foundation Trust, United Kingdom, \(^21\)University Hospital Cente Zagreb, University Department of Neurology, \(^22\)University Hospital in Krakow, Poland, \(^23\)University Hospitals Leuven, Belgium, \(^24\)University Medical Center Groningen, Netherlands, \(^25\)University Medical Centre Ljubljana, Slovenia, \(^26\)University of Pécs, Hungary, \(^27\)Patient representative

**Flowchart development process:**

- Development of flowchart – September 2019 – July 2020
- Consent on document by whole disease group – July 2020
In EOA consider:
1) Previous history including family history
2) Clinical evaluation including:
   - Assessment of Inventory of Non-Ataxia Symptoms (INAS)
   - Grading of ataxia: clinical scale (e.g. SARA)
3) Perform **brain MRI and Neurophysiology**

- **Exclude ataxia**
- **Exclude acquired**

**Reasses**

- No specific abnormalities
  - Consider test for Repeat
  - WES-WGS

- Family History or Distinct Phenotype or dysmorphism
  - Laboratory Investigations, +/- aCGH or aSNP

**If negative**
- mtDNA seq
- aCGH/aSNP, karyotype
- WES-WGS reanalysis

**If**
- Single-gene direct sequencing or
Notes:
WES-WGS could be initiated, if timely available, parallel to the investigations following brain MRI
*Distinct EOA phenotypes and targeted investigations reviewed in Brandsma R et al., Eur J Paediatr Neurol 2019

Abbreviations:
aCGH – microarray-based Comparative Genomic Hybridisation
aSNP – microarray-based testing for Single Nucleotide Polymorphisms
mtDNA seq – Mitochondrial DNA sequencing
MRI – Magnetic Resonance Imaging
NGS – Next Generation Sequencing
WES – Whole Exome Sequencing
WGS – Whole Genome Sequencing