The Pediatric Cerebellum in Inherited Neurodegenerative Disorders

A Pattern-recognition Approach

Susan I. Blaser, MD[a,*], Maja Steinlin, MD[b], Almundher Al-Maawali, MD[c], Grace Yoon, MD[d]

KEYWORDS

• Cerebellum • Inborn errors of metabolism • Inherited neurodegenerative disorders

KEY POINTS

- Accurate genetic diagnosis of childhood-onset cerebellar ataxia is complicated by both clinical and genetic heterogeneity.
- Neuroimaging assessment of the cerebellum should include degree of volume loss, gradient of atrophy, signal intensity, magnetic resonance spectroscopy, and change over time.
- Integration of neuroimaging patterns with clinical information is essential to appropriate investigation of childhood-onset cerebellar ataxia.

INTRODUCTION

Inherited neurodegenerative disorders resulting from genetic and inborn biochemical defects can affect the cerebellum at any time, either during development and maturation or later in life. The resultant imaging appearance of the posterior fossa structures can reflect growth arrest (prenatal), growth arrest with superimposed atrophy (prenatal and postnatal), or either stable or progressive cerebellar atrophy (postnatal). Imaging features also include swelling or gliosis, calcification, diffusion restriction, enhancement, cysts, or alterations in magnetic resonance (MR) spectra. Additional features (eg, hyperintensity of the dentate nuclei or cerebellar cortex; specific volume loss patterns of the brainstem, vermis, and cerebellar hemispheres; swelling of the cerebellar white matter; change over time; and involvement of the supratentorial compartment) are crucial in narrowing the differential diagnosis.[1,2] Despite the rapidity with which genetic diagnoses may be made with the decreasing cost and increasing availability of whole-exome sequencing (WES), there are limitations with regard to complete coverage of all coding regions, and difficulties with large genomic rearrangements, trinucleotide repeat sequences, and interpretation of variants.[3] In 2 studies involving pediatric subjects, WES provided genetic diagnoses for 39% and 46% respectively of patients with previously undiagnosed childhood-onset cerebellar ataxia. Diagnosis in the remainder remained occult.[4,5] In another study

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[a] Division of Paediatric Neuroradiology, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada; [b] Division of Neuropaediatrics, Development and Rehabilitation, University Children's Hospital Inselspital, University of Bern, Freiburgstrasse 4, Bern 3010, Switzerland; [c] Department of Genetics, Sultan Qaboos University Hospital, Al Khoudh, Muscat 123, Oman; [d] Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada

* Corresponding author.

E-mail address: susan.blaser@sickkids.ca

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of 126 patients referred for progressive cerebellar ataxia, genetic testing was not always positive.[6] Imaging therefore remains an important tool in the diagnosis, staging, and assessment of therapy for neurodegenerative disorders affecting the cerebellum (**Boxes 1** and **2**).

NEUROIMAGING PATTERN COMPONENTS IN THE CEREBELLUM

Neuroimaging patterns include combinations of: varying degrees of cerebellar volume loss; gradients of volume loss; signal intensity (swelling or gliosis/shrinkage) of the cerebellar cortex or white matter, dentate nuclei, brainstem tracts, and nuclei; diffusion restriction; enhancement; cysts; brain iron or calcifications; specific supratentorial patterns; and MR spectroscopy (MRS) spectra of the supratentorial compartment, cerebellum, or brainstem. The concept of selective vulnerability, caused by the different affinity of noxious insults to different brain structures at differing developmental stages, remains pertinent when discussing the cerebellum. Thus, the appearance at the time of presentation and any change in pattern with further brain development contribute important clues[7–9] (**Box 3**).

BIOMETRY

Multiplanar planimetry, assessing regional length, height, and area of the mesencephalon, pons, medulla, and cerebellar peduncles, adds a degree of specificity in baseline and follow-up assessment in patients with inborn errors of metabolism involving the cerebellum. Although measurements of the mesencephalon are slightly less reproducible because of the variability of slice thickness and partial volume averaging with the interpeduncular cistern, measurements performed on a midsagittal

Box 1
Imaging and evaluation protocols

- Image in all 3 orthogonal planes (three-dimensional techniques with multiplanar reconstruction may be used)
- Routine T1/T2 with age-appropriate sequence modification; fluid-attenuated inversion recovery (FLAIR)
- Diffusion-weighted imaging (DWI) or diffusion tensor imaging (DTI)
- Sequence sensitive to calcium, hemosiderin, and brain iron: T2*/Multiplanar Gradient-Recalled/Susceptibility Weighted Imaging
- Contrast administration may be helpful if abnormal signal on routine sequences
- MR spectroscopy (MRS)
  - Supratentorial: deep gray/white matter
  - Cerebellum/brainstem

Box 2
Imaging features contributing to patterns of inherited neurodegenerative disorders involving the cerebellum

- Degree of volume loss (or gain)
  - Vermis, cerebellar hemispheres, interfoliate fissures
  - Cerebellar peduncles
  - Brainstem
    - Mesencephalon
    - Pons
    - Medulla
  - Spinal cord
- Gradient of atrophy
  - Superior versus inferior vermis predominant
  - Vermis versus cerebellar hemisphere predominant
  - Cisternal enlargement
- Signal intensity (swelling or gliosis/shrinkage)
  - Cerebellar cortex
  - Cerebellar nuclei (predominantly dentate)
  - Cerebellar white matter
    - Middle cerebellar peduncles
    - Peridentate cerebellar white matter
    - Dentate hilar white matter
  - Brainstem tracts
- Additional imaging clues
  - Diffusion restriction
  - Specific supratentorial white matter patterns
  - Brain iron (dentate, supratentorial gray matter nuclei)
  - Foci of magnetic susceptibility
    - Telangiectasias
    - Hemosiderin
    - Calcifications
    - Brain iron
  - Other: cysts, enhancement
  - Other: chiasmatic enlargement (Krabbe/*GALC*) or atrophy (optic atrophy 1/*OPA1*)
  - Other: change over time
  - MRS: infratentorial, supratentorial