Radiological Aspects of Genetic Disorders with Adult-onset CNS Symptoms

R. RAININKO\textsuperscript{1}, A. MELBERG\textsuperscript{2}

\textsuperscript{1}Departments of Radiology and Neuroscience, \textsuperscript{2}Neurology, Uppsala University, Uppsala, Sweden

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**Introduction**

Genetic disorders affecting the central nervous system have a wide age range regarding onset of symptoms. A specific disease entity may have childhood onset or adult onset forms, whereas other disease entities may only yield symptoms in adulthood. Symptoms may be neurological or psychiatric including early dementia. It is important to recognize such diseases because the correct diagnosis may yield information on the mode of inheritance, prognosis and have an impact on the patient’s treatment. Radiological examinations also provide further knowledge about these diseases and help us in understanding pathophysiology. Examples of some genetic diseases with adult-onset will be presented.

*Mitochondrial disorders* are often paediatric diseases but may have an onset at any age, sometimes with first symptoms later than the sixth decade. A wide range of organs may be involved including the brain, skeletal muscle, heart and endocrine organs. The course may be static, progressive or with episodes of exacerbation. Maternally inherited MELAS (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) and autosomal recessive \textit{POLG1}-associated encephalopathy syndromes are examples of such diseases. In both syndromes, stroke-like episodes occur and stroke-like lesions are found on MRI.

In autosomal recessive \textit{POLG1}-associated syndromes\textsuperscript{1}, the changes are often cortical (but rarely in the temporal lobes) and thalamic (Figure 1). Cerebellar lesions may occur. Patients affected by autosomal recessive \textit{POLG1} mutations may present with epilepsy (with episodes of focal status epilepticus) and stroke-like episodes and may develop ataxia, ophthalmoplegia and sensory neuropathy. Valproate should be avoided in treating the epilepsy of these patients because it may cause severe liver damage. In a dominantly inherited \textit{POLG1} form, the clinical symptoms are different with progressive external ophthalmoplegia (PEO), muscular weakness, premature menopause, parkinsonism and ataxia\textsuperscript{2}. Diagnosis is made by demonstrating signs of mitochondrial myopathy and multiple mitochondrial DNA deletions in skeletal muscle biopsy specimens and sequencing the \textit{POLG1} gene\textsuperscript{3}.

Patients with \textit{hepatolenticular degeneration} (Wilson’s disease) have a defect in copper metabolism and may present hepatic (in particular in children) or neurological symptoms or dementia\textsuperscript{4}. The latter symptoms are more dominant in the adult forms. The patients have tremor, speech disorders, clumsiness, dystonia and personality changes. Inheritance is autosomal recessive. Aids in diagnosis are ophthalmological examination for Kayser-Fleischer rings, measuring ceruloplasmin and copper in serum, copper excretion in the urine and liver biopsy including copper content. Genetic analysis of the \textit{ATP7B} gene is also possible. Typical MRI findings are high T2 signal intensity in the basal ganglia, thalami and mesencephalon. These patients may also have cerebral and cerebellar white matter changes which can be asymmetric (Figure 2). The high T2 signal intensities decrease during the treatment (Figure 3).

\textit{Polycystic lipomembranous osteodysplasia and sclerosing leukencephalopathy} (PLOS, \textit{Nasu-Hakola disease}) is an example of the disease which first affects the bones but later gives brain symptoms\textsuperscript{5}. The first symptom is pain in bones and the patients often have

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Figure 1 An 18-year-old man with autosomal recessive POLG1 mutations. The patient was hospitalized for status epilepticus. A) A pathologic area with an appearance of an ischaemic lesion in the right occipital lobe (arrow) on CT. B) Two days later, a lesion is also seen in the right thalamus. C-E) MRI was performed four days after the hospitalization. Diffusion-weighted images (b=1000) revealed lesions also in the right parietal and frontal lobes. F-G) Only the thalamic lesion was visible in the FLAIR images. H) Two months and three weeks later, the thalamic lesion was still demonstrable but the other lesions had disappeared. FLAIR image.
Figure 2  A 22-year-old man with symptoms of dementia. He had Wilson’s disease. T2-weighted SE images show high signal intensities in the basal ganglia, thalami and brain stem. The “panda eyes” in the mesencephalon are a typical finding. Hyperintense areas in cerebral and cerebellar white matter. Note the asymmetry of the cerebral white matter pathology.

Figure 3  T2-weighted SE images of a 34-year-old man with a treated Wilson’s disease. Hyperintensity of the lesions decrease during the treatment.
pathological fractures due to bone cysts. Dementia develops about at the age of 30 and the patients die before the age of 50. Inheritance is autosomal recessive and mutations have been shown in the DAP12 or TREM2 genes. Diagnosis can be made on the basis of clinical and radiological findings. Bone cysts are revealed in radiograms of the wrists and ankles (Figure 4). Atrophy of the caudate nuclei and calcium deposits in the basal ganglia, mainly in the putamina, are typical first radiological findings (Figure 5). Atrophic changes become general in the cerebrum but may also occur in the cerebellum. Diffuse T2 signal intensity increase can be revealed on MR images. They are situated mainly in the deep cerebral white matter (Figure 6) but can extend up to the cortex.

Leukodystrophies most often manifest in infants and children but there are also adult types. Inheritance is most often recessive but there are also sporadic forms and some leukodystrophies are x-linked. Adult-onset forms and dominant inheritance are uncommon.

Adult-onset metachromatic leukodystrophy typically begins in young adults and with psychiatric symptoms. Diagnosis is made by demonstrating reduced activity of arylsulfatase A in peripheral leukocytes and increased excretion of sulfatides in the urine. The patients have different types of mutations in ARSA gene. MRI
reveals high T2 signal intensity in the corpus callosum and periventricular white matter (Figure 7). The thalamic T2 signal intensity is low as usually in lysosomal diseases. There are also adult-onset forms of Krabbe disease (globoid cell leukodystrophy) and of Alexander disease. Their radiological findings are different from those seen in infantile or childhood types. In adult-onset Krabbe disease, the patients may have spastic paraparesis or hemiparesis. Diagnosis is made by demonstrating deficient galactocerebroside activity in leukocytes. Mutations are present in the GALC gene and the disorder is autosomal recessive. The increased T2 signal is first found in the uppermost part of the pyramidal tract (Figure 8) and affects the entire pyramidal tract in the brain. The spinal cord is thin (Figure 9) but white matter signal intensity changes have not been reported in the cord.

In adult-onset Alexander disease, the patients have diverse symptoms and episodic or progressive course. They may have bulbar and pseudobulbar symptoms, spasticity, ataxia, dementia, nystagmus and palatal myoclonus. The patients have a heterozygous GFAP mutation and diagnosis is aided by genetic test. Almost all cases are sporadic but an autosomal dominant form exists. MRI may show a high T2 signal intensity periventricularly (Figure 10A) but the most characteristic changes are situated in the medulla oblongata and upper spinal cord (Figure 10B-E). There is local or diffuse signal intensity increase and, in active periods, patchy contrast enhancement may occur. Development of atrophy in the medulla oblongata and upper cervical cord is very typical. The entire spinal cord may be atrophic and the white matter has a pathological high signal intensity (Figure 10F-G).
Patients with adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms present first clinical symptoms in the fifth to sixth decade. Autonomic symptoms (bladder and bowel dysfunction, orthostatic dysfunction) usually precede cerebellar and pyramidal signs. The genetic error is the duplication of Lamin B1 gene with subsequent overexpression. Diagnosis is based on clinical symptom constellation and characteristic MRI findings. The diagnosis can be completed with genetic analysis. The mildest radiological abnormality is a high T2 signal in the upper pyramidal tract (Figure 11) and then the signal abnormality spreads downwards along the pyramidal tracts, into the periventricular area and also into the middle cerebellar peduncles (Figure 12). These findings can be revealed in asymptomatic family members. Symptomatic patients have widespread cerebral white matter changes (Figure 13). Characteristically, there is a less affected area just around the lateral ventricles. Substance loss is mild in the brain. The spinal cord is thin and the entire spinal cord white matter emits a high T2 signal even in asymptomatic subjects (Figure 14).

Some disorders primarily affect blood vessels. One example is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The age at onset is about 50 years. The patient should have at least two of these symptoms: stroke-like episodes with permanent neurological signs, migrainous headache, major mood disturbances or subcortical dementia. Diagnosis is made by skin biopsy and demonstrating granular osmiophilic material (GOM) in vascular smooth muscle cells. The etiology is a mutation in the
NOTCH3 gene. MRI reveals periventricular white matter changes. Characteristically, the temporal white matter which often is the best preserved part of the brain in vascular white matter diseases is affected in CADASIL (Figure 15). Involvement of the external capsules is also typical. Those changes develop before clinical symptoms. Old lacunar infarcts are often seen as black holes in the deep white matter. MR imaging with T2*-weighting gradient echo sequences or a SWI sequence often reveals microhaemorrhages, most often in central areas.

Microbleeds are also seen in cerebral amyloid angiopathy in which both sporadic and familial forms exist. In that disease most bleedings are situated more peripheral. Microbleeds and cavernomas type IV may have an identical appearance. There is a familial form of multiple cavernomas which is genetically heterogenous. Cavernomas can be found both in the brain (Figure 16) and spinal cord (Figure 17) and they can be of different cavernoma types. Cavernomas enhancing after contrast administration are easier to recognize than cavernomas type IV which did not show contrast enhancement.

There are several genetic disorders in which there may be more or less typical findings. One disease is presented as an example: hereditary spastic paraparesis with thin corpus callosum (HSP-TCC). Inheritance is autosomal recessive and the disease is genetically heterogenous. In 35% of the cases, the mutation is found in the SPG11 or SPG15 genes. The symptom onset is in the first to third decade. The patients have spastic paraparesis, cognitive decline and amyotrophy. The patients with SPG11 mutations also have central retinal degeneration.
Figure 9 Spinal cord atrophy in the same patient as in Figure 8.

(Kjellin syndrome)\textsuperscript{17}. Diagnosis is based on clinical constellation and the MRI findings. The gene involved may be obtained by genetic linkage analysis or sequencing the two most common candidate genes SPG11 and SPG15. On MRI, these patients have progressive brain substance loss with general enlargement of the lateral and third ventricles and locally variable peripheral cerebral atrophy (Figure 18). Cerebellar atrophy has also been reported. Cerebral T2 signal intensity is increased, mostly in central areas. The signal intensity increase is slight and may easily be interpreted as low image quality in early phase of the disease (Figure 19). These are very nonspecific changes. The corpus callosum is very thin even at the time of the first symptoms but slight progress has been demonstrated. The splenium is less affected than the other parts. As a curiosity,
all the patients with SPG11 mutations, even those without pathologic MRI findings other than the thin corpus callosum, had T2 hyperintense bundles anterior to the frontal horns (Figures 18-19).

A thorough and systematic analysis of the atrophic and signal intensity changes may help to establish a specific diagnosis or at least to rule out diseases with similar clinical symptoms and clinical findings. Collaboration with geneticists and clinical neurologists is of great importance in evaluating specificity of radiological diagnosis. One should also remember that radiological abnormalities may precede clinical symptoms and may be found in asymptomatic individuals.

References


Figure 11  An asymptomatic 37-year-old man from a family with adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms. Increased signal intensity in the pyramidal tract on FLAIR images. From Ref.10 with permission.

Figure 12 An asymptomatic 34-year-old man from a family with adult-onset ADLD with autonomic symptoms showing a very high signal intensity in the parietal and frontal white matter and in the cerebellar peduncles. T2-weighted SE images. From Ref. 10 with permission.
Figure 13 A 55-year-old patient with adult-onset ADLD with autonomic symptoms shows even larger hyperintense areas. A less affected layer around the lateral ventricles is characteristic. From Ref.6 with permission.

Figure 14 In adult-onset ADLD with autonomic symptoms, the spinal cord is atrophic and the entire white matter has a high T2 signal intensity.
Figure 15  FLAIR images of a 47-year-old woman having CADASIL. Note that there are high signal intensity areas in the temporal lobes and external capsules. Old lacunar infarcts are also typical findings.

Figure 16  Multiple cavernomas, autosomal dominant form. A 21-year-old woman with numbness in the right leg. Her brother had had a bleeding in the spinal cord, T2-weighted FSE images did not show any pathology (A) but on T2*-weighted gradient echo images, a microhaemorrhage/cavernoma was detected in the right cerebellar hemisphere (B). No contrast enhancement could be seen (C) and the lack of contrast enhancement is characteristic for cavernoma type IV. A SWI sequence revealed a couple additional cavernomas in the cerebrum.
Figure 17 Spinal images of the same patient as in Figure 16. A cavernoma was demonstrated on T2*-weighted images (A-B) but could not be recognized on T2-weighted FSE images (C). No contrast enhancement could be seen.

Figure 18  MR images of hereditary spastic paraparesis with thin corpus callosum (HSP-TCC) with mutations in the SPG11 gene. The same patient at the ages of 34 (A-D) and 46 (E-H). Very thin corpus callosum which has become even thinner during the follow-up (A,E). Progressive substance loss is not symmetrical and varies locally. Small hyperintense bundles anterior to the tips of frontal horns. From Ref.15 with permission.

Figure 19  In a 18 year-old patient with SPG11-related HSP-TCC, the signal intensity increase is very diffuse and difficult to detect. Even in this case, the corpus callosum is very thin and the bundles anterior to the frontal horns well detectable.

R. Raininko, MD, PhD
Department of Radiology - University Hospital
751 85 Uppsala, Sweden
Tel.: +46-18-611 47 80 (office) - +46-18-611 47 57 (secretary)
+46-708-62 45 04 (mobile) - Fax: +46-18-55 12 65
E-mail: Raili.Raininko@radiol.uu.se