Cerebellar Disorders—At the Crossroad of Molecular Pathways and Diagnosis

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Published online: 27 October 2009
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Abstract Our understanding of the pathogenesis of cerebellar ataxias has started several decades ago and is continuously growing. The numerous mechanisms of cerebellar dysfunction are being discovered by numerous groups of researchers worldwide. Neuronal damage results from a complex interaction of metabolic pathways, which leads to symptoms observed in cerebellar disorders. The main mechanisms at the molecular level are the following: impairment of DNA repair and replication, deregulation of transcription/deficits of processing/transport of RNA, abnormal protein transport and misfolding, aggregates both at the nuclear and cytosolic level, activation of caspases, apoptosis, involvement of autophagic mechanisms, oxidative stress and mitochondrial dysfunction, excitotoxicity, abnormal lipid metabolism, impaired axonal transport and vesicle trafficking, and defects of the neurotransmission. The convergence of the current clinical classification with molecular findings is expected. This integration is a basic substrate for the rationale development of therapies.

Keywords Cerebellum · Ataxias · Pathogenesis · Diagnosis

Cerebellar ataxias are being growingly recognized worldwide. Cerebellar disorders include a group of heterogeneous disorders with noticeable overlap between entities, including sporadic and hereditary ataxias [1, 2]. These latter are often divided into recessive ataxias, dominant ataxias, ataxias related to a mitochondrial disorder which affect oxidative phosphorylation in most cases, and X-linked ataxias. Dominant ataxias include the wide spectrum of so-called spinocerebellar ataxias (SCAs/ADCA: autosomal dominant cerebellar ataxias, divided in several types according to Harding's classification). The most common diseases are summarized in Table 1. A diagnostic tree is proposed to the reader (Fig. 1).

Major breakthroughs in our understanding of the pathogenesis of cerebellar ataxias have been reached thanks to technical advances and the elaboration of relevant cellular and animal models, these latter reproducing to various extents human brain disorders. At the molecular level, the main discoveries of these last 25 years in terms of pathogenesis of cerebellar disorders can be grouped as follows in subcategories:

1. Deficits in DNA repair
2. Transcriptional deregulation
3. Accumulation of toxic proteins or decreased clearance of proteins
4. Misfolding
5. Caspase activation
6. Apoptosis
7. Primary or secondary mitochondrial dysfunction
8. Oxidative stress
9. *N*-methyl-D-aspartate (NMDA)-mediated excitotoxicity and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated excitotoxicity
10. Disturbances at the lysosomal level

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Table 1 Most common cerebellar disorders

1. Sporadic ataxias
Structural disorders—malformations
Neurodevelopmental disorders
Immune disorders (multiple sclerosis, cerebellar ataxia with anti-glutamic acid decarboxylase antibodies, gluten ataxia, Miller–Fisher syndrome, systemic lupus erythematosus, Sjögren syndrome)
Infections
Vascular disorders (stroke: ischemia, hemorrhage)
Intoxication (ethanol, drugs) and environmental causes
Ataxias of endocrine origin (thyroid dysfunction)
Primary neoplasias (medulloblastomas, astrocytomas, ependymomas, meningiomas, lymphomas, histiocytosis) and metastases
Paraneoplastic ataxia (anti-Yo, anti-Hu, anti-Ri, anti-Tr, anti-CV2 antibodies)
Idiopathic late-onset ataxia
Cerebellar form of multiple system atrophy (cMSA)
Superficial siderosis
Migraine
2. Genetic ataxias
<i>Recessive disorders</i>
Friedreich ataxia (FA)
Vitamin E deficiency
Ataxia with vitamin E deficiency (AVED)
Abetalipoproteinemia (ABL)
Cholestatic liver disease
Intestinal resection
Ataxia with ocular motor apraxia (AOA1, AOA2)
Refsum disease (RD)
Cerebrotendinous xanthomatosis (CTX)
Early onset cerebellar ataxia with retained reflexes (EOCARR)
Ataxia-telangiectasia (AT) and related disorders
Deficiency in Coenzyme Q10
Autosomal-recessive spastic ataxia of Charlevoix–Saguenay (ARSACS)
Marinesco–Sjögren syndrome (MSS)
Wilson’s disease
Aceruloplasminemia
Niemann–Pick type C
Late-onset Tay–Sachs disease (LOTS)
ARCA
Ataxia with hypogonadism
Ataxia and optic atrophy (Behr syndrome)
Progressive myoclonic epilepsies
Karak syndrome
Spinocerebellar ataxia with axonal neuropathy (SCAN1)
Infantile-onset spinocerebellar ataxia (IOSCA)
Mitochondrial recessive ataxia syndrome (MIRAS; POL γ mutations)
Xeroderma pigmentosum
Hartnup disease

Table 1 (continued)

Maple syrup disease
Carnitine acetyltransferase deficiency
Hydroxyglutaric aciduria
Congenital forms
Joubert syndrome
Cayman ataxia
COACH syndrome
Pontocerebellar hypoplasia
Ataxic cerebral palsy
<i>Dominant disorders</i>
Spinocerebellar ataxias (SCAs, 1–30)
Pure cerebellar syndrome (SCA5, 6, 11, 26)
Cerebellar ataxia-plus
Episodic ataxias (EAs, EA1–7)
Dominantly inherited spastic ataxia syndromes
Spastic paraplegia, ataxia, mental retardation (SPAR)
Ataxia/spasticity with congenital miosis
Myelocerebellar syndrome
Cerebellar ataxia, deafness and narcolepsia
Essential tremor (sporadic forms exist also)
Von Hippel–Lindau syndrome (VHL)
<i>Mitochondrial disorders</i>
Kearns–Sayre Syndrome
May–White Syndrome
MNGIE (ophthalmoparesia, peripheral neuropathy, and gastrointestinal symptoms), Leigh syndrome
NARP (neuropathy, ataxia, and retinitis pigmentosa)
MELAS (mitochondrial encephalomyopathy, lactic acidosis with stroke-like episodes)
MEERF (myoclonus epilepsy with ragged red fibers).
<i>X-linked ataxias</i>
Fragile-X tremor ataxia syndrome
Arts syndrome
X-linked adrenoleukodystrophy (X-ALD)
Rett syndrome
Ataxia-dementia
Ataxia-Deafness syndrome
Sideroblastic anemia and spinocerebellar ataxia (ABC7)
Deficit in pyruvate dehydrogenase E1-alpha
Pelizaeus–Merzbacher allelic variant

11. Abnormal fatty acid metabolism

12. Disorders of neurotransmission

Figure 2 illustrates these pathways. A main field of investigations is on SCAs. Currently, 28 SCAs are identified [3]. In several SCAs, the expansion of CAG tracts in certain genes results in transcription of proteins with abnormally long polyQ (polyglutamine) inserts [4]. Such a mechanism is shared with Huntington’s disease

Fig. 1. Diagnostic algorithm of cerebellar disorders. The assessment of a patient with a suspicion of a cerebellar disorder is illustrated. Abbreviations: *EA* episodic ataxias, *SCA* spinocerebellar ataxia (previously identified as *ADCA* autosomal dominant spinocerebellar ataxia), *FA* Friedreich ataxia, *LOFA* late-onset Friedreich ataxia, *FARR* Friedreich ataxia with retained tendon reflexes, *VLCFA* very long-chain fatty acid, *EEG* electroencephalography, *EP/NCV* evoked potentials, nerve conduction velocities, *CSF* cerebrospinal fluid, *FXTAS* fragile X tremor/ataxia syndrome, *MSA/sOPCA* multiple system atrophy/sporadic olivopontocerebellar atrophy, *ILOCA* idiopathic late-onset cerebellar atrophy, *CJD*: Creutzfeldt–Jakob disease, *GSS* Gerstmann–Sträussler–Scheinker disease

(HD) and spinal bulbar muscular atrophy (SBMA). Proteins form aggregates which contribute to neuronal loss. Expanded polyQ tracts participate in the formation of partially unfolded proteins [4]. Neurological deficits of polyQ repeat disorders appear for expanding tracts exceeding the critical value of 35–45 glutamines [4, 5]. Several models have been developed to recapitulate the molecular mechanisms occurring in cerebellar disorders, ranging from in vitro studies to complex animal models, each of them having advantages and disadvantages for translational research [6]. In vitro experiments indicate that proteasomes are unable to digest

polyQ tracts [7]. Aggregates sequester proteasomes, ubiquitin, polyQ fragments and recruit HSP70 [7]. Therefore, essential proteins are depleted from the cells, an event which contributes to cell vulnerability [7]. Expanded polyglutamine tracts decrease the dimerization of TBP (TATA box protein) and enhance the binding to the transcription factor TFIIB [3]. The consecutive depletion of TFIIB is another factor causing neural susceptibility. SCA7 is an example of cerebellar disorder associated with defects of acetylation/deacetylation [8]. Mutant ataxin-7 targets the process of chromatin remodeling, causing

transcriptional down-regulation. Ataxin-7's normal function as a transcription factor may explain the selective vulnerability of specific neuronal populations in SCA7 [9]. Other proteins, such as ataxin-1, involve both transcriptional regulation and RNA splicing [3]. Ataxin-2 interferes with the metabolism of RNA as a result of an interaction at the level of polyribosomes [10]. Ataxin-3 is also implicated in transcriptional deregulation. The protein acts as a repressor of transcription [3]. Ataxin-3 is closely linked to the

phenomenon of ubiquitination/deubiquitination [11]. Protein cleavage is caspase-dependent and this cleavage boosts neuronal loss, suggesting that therapies targeting the cleavage of ataxin-3 might slow the disease progression in SCA3 [12].

Impairment of neurotransmission is another mechanism shared by several cerebellar disorders. Impairment of glutamatergic/calcium signaling has been pointed in various sporadic and genetic ataxias, including SCA6, SCA13, or

◀ **Fig. 2.** Molecular pathways involved in hereditary cerebellar ataxias and which contribute to DNA/RNA/protein defects ending in cell death. Several neurons are illustrated, as well as a glial cell. The various pathophysiological processes may involve some specific categories of cells, according to the disease considered. In some disorders, the molecular pathogenesis still remains to be elucidated. In some instances, organelles are represented in association with a specific disorder, when this latter is critically linked to the given intracellular element, such as mitochondria for Friedreich ataxia (*FA*). Key-mechanisms affect DNA, RNA, apoptosis, impairment of proteasome degradation, calcium homeostasis, mitochondrial dysfunction, axonal transport, trafficking of vesicles, excitotoxic cascades/oxidative damage, dysfunction of ion channels, deficits of neurotransmission. Abbreviations: *SBMA* spinal bulbar muscular atrophy, *HD* Huntington's disease, *DRPLA* dentatorubral-pallidoluysian atrophy, *FMR2* fragile X mental retardation gene, *TATA* TATA box binding protein, *POLII* RNA polymerase II, *HSP* heat shock proteins, *Ub* ubiquitin; Mitochondria: *Polγ* polymerase-gamma, *mtDNA* mitochondrial DNA, *SOD* superoxide dismutase, *GPX* glutathione peroxidase, *ABC7* ATP-binding cassette 7, *AVED* ataxia with vitamin E deficiency, *CACNA1A* voltage-dependent calcium channel P/Q type (alpha 1A subunit); *KCNC3* potassium voltage-gated channel (subfamily C member 3), *SERCA* Sarco/endoplasmic reticulum Ca²⁺-ATPase, *ITPR1* inositol 1,4,5-triphosphate receptor (type 1), *HDL* high-density lipoprotein, *VLDL* very low-density lipoprotein, *IDL* intermediate-density lipoprotein

SCA27. SCA6 is associated with a CAG expansion in the CACNA1A subunit of the voltage-gated calcium channel P/Q CaV2.1. Increase in calcium signaling contributes to a gain-of-function, as well as translocation of a fragment to the nucleus [3, 13]. The glutamate transporter EAAT4 is stabilized by beta-III spectrin, whose mutations cause SCA5 [14]. Decreased reuptake of glutamate contributes to the cascade of NMDA and AMPA-mediated excitotoxicity [15]. Further studies are needed to confirm that SCA20 is also related to an overflow of glutamate [3, 16]. Mutations of the KCNC3 voltage-gated potassium channel (SCA13) affect directly the depolarization of neuronal membranes.

We are at the beginning phase of the integration of the clinico-genetic classification with molecular pathways involved in the pathogenesis of each family or subtype of cerebellar disorders. A reshaping of the clinico-genetic classification taking into account the molecular discoveries is likely to emerge soon. This fusion would have important consequences in terms of management, therapies, and future investigations in cerebellar research. In most cases, therapies of devastating ataxic disorders have remained purely symptomatic, because of (1) the lack of understanding of the molecular deficits, (2) the inability to identify the critical pathway(s) for each disorder, and (3) as a result of the use of models of cerebellar disorders which have brought non-relevant information for the development of therapies. Several therapeutic lines have now been drawn: modulation of gene expression and transcriptional tuning, changing the clearance of a mutant protein, making the

protein less toxic, action upon chaperones, use of transglutaminase inhibitors, effects on caspase activation, effects on mitochondrial function and oxidative damage [17]. Development of therapies of sporadic ataxias might take an unexpected benefit from these investigations. The reverse is also true. For instance, there is hope that looking beyond the traditional mechanism of glutamate-receptor-driven excitotoxicity could be very useful in stroke models [18]. There are growing evidence that ionic imbalance contributes to cell death; hence, the ongoing studies on sodium-calcium exchangers, hemichannels, volume-regulated anion channels, acid-sensing channels, transient receptor potential channels, nonselective cation channels, and signaling cascades [18]. New insights in the molecular pathogenesis of sporadic and hereditary ataxias open also now doors towards the unraveling of the myriad of secrets of the cerebellar circuits.

Acknowledgements M.M. is supported by the FNRS-Belgium, D.M. is supported by the Fonds Erasme-Belgium.

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