

# Problems and possibilities in the differential diagnosis of Syndrome Spinocerebellar Ataxia

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MOTTO: NULLA REGULA SINE EXCEPTIO

## Abstract

Differential diagnosis in neurologic patients with spinocerebellar syndrome is complex as a result of the great degree of variability in phenotypic and genetic aspects of more than 200 nosological entities. In the past decade, genetic etiology has been discovered in part of the diseases and the term "spinocerebellar ataxia" has become, from a neurologic point of view, a loose definition applied to a group of autosomal dominant diseases. Topical extensive literature about differential diagnoses of ataxias usually refers to genetics classification or is produced by a group of radiologists, elektrophysiologists and biologists as well as others in the field. A further problem is that the majority of studies do not take into account other acquired illnesses and diseases which may fundamentally alter the symptomology and course of a primary disease, not to mention the possibility of concomitancy in hereditary diseases. The following article was prompted by daily contact with ataxic patients and related issues raised by colleagues; its goal is to clarify problems faced by child neurologists and neurologists in clinical practice.

## Abbreviation and units:

AD – Autosomal dominant  
ADCA – Autosomal dominant cerebellar ataxia  
ALS – Amyotrophic lateral sclerosis  
AR – Autosomal recessive  
AT – Ataxia teleangiectasia  
AVED – Ataxia with Vitamin E Deficiency  
BAEP – Brain auditory evoked potential  
CAG – Cytosine Adenine Guanine  
CNS – Central nervous system  
CT – Computer Tomography  
CTG – Cytosine Thymine Guanine  
Cu – Copper  
DNA – Deoxyribonucleic acid  
DRPLA – Dentatorubropallidoluysian atrophy  
ECG – Electrocardiogram  
EEG – Electroencephalogram  
EMG – Electromyography  
EOG – Electro-oculography

EOCA – Early-onset cerebellar ataxia with retained reflexes  
ENG – Electro-nystagmography  
FRDA – Friedreich's ataxia  
FXTAS – Fragile X Premutation Tremor/Ataxia Syndrome  
HAM – Hearing loss, Ataxia, Myoclonus (epilepsia partialis continua)  
HSAN – Hereditary sensory autonomic neuropathy  
HSMN – Hereditary sensory motoric neuropathy  
IOSCA – Infantile-onset cerebellar ataxia  
L – Lumbar  
LDL – Low-density lipoprotein cholesterol  
MELAS – Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke like episodes  
MEP – Motor evoked potentials  
MERRF – Myoclonic Epilepsy, Ragged Red Fibers  
MRI – Magnetic Resonance Imaging  
NARP – Neuropathy, Ataxia, Retinitis Pigmentosa  
NCL – Neuronal ceroid lipofuscinosis  
PANK 2 – Pantothenate kinase 2

S	– Sacral
SCA	– Spinocerebellar ataxia
SEP	– Somatosensory evoked potentials
SMNA	– Autosomal dominant sensory/motor neuropathy with ataxia
SNE	– Subacute Necrotizing Encephalopathy
US	– Ultrasound
VEP	– Visual evoked potential
VLCFA	– Very long chain fatty acid
VLDL	– Very low density lipoproteins

## INTRODUCTION

Orientation within the group of neurodegenerative disorders has always presented difficulties and lacked transparency.

One demonstrative example is that as early as 1953 Cobb and Bereday made an attempt *to organize the chaos* in neurological literature by pointing out that eight main syndromes existed among the more than fifty clinical depictions that had been outlined among the familial system diseases. The past repeats itself – practically 50 years later, in 2002, Margolis [31] published an article entitled *The Spinocerebellar Ataxias: Order Emerges from Chaos*.

The history of the concept of ataxia in the modern period begins with the first descriptions of the main degenerative ataxic disorders: Friedreich's ataxia between 1863–1877 and Strumpel's hereditary spastic paraplegia between 1886–1924. Pierre Marie recognized cases distinct from Friedreich's ataxia in 1893. Déjérine and Thomas introduced the term olivopontocerebellar atrophy in 1900. Fifty years later, Greenfield compiled the first comprehensive ataxia classification. Basing his classification on pathological criteria, he divided heredoataxias into three groups of predominantly spinal, spinocerebellar, and cerebellar forms. Pathological classification of the ataxia, however, is not helpful to clinicians – we must attempt to establish diagnosis *in vivo*. The final functional classification is in Harding's pre-DNA testing era classification, which proposed starting with clinical and genetic features. Harding [19] divided hereditary ataxias and paraplegias into four groups, numbered I–IV. These were as follows: I) Congenital disorders of unknown etiology, II) Ataxic disorders with known metabolic or other cause, III) Ataxic disorders of unknown etiology, and IV) Hereditary spastic paraplegia. Early and late onset cerebellar ataxias were distinguished in group III. The subgroup III B – late onset – includes four types of autosomal dominant cerebellar ataxias which are assigned the classification ADCA I–IV.

In the past decade, the genetic etiologies accounting for many cases of dominant cerebellar ataxia have been discovered. They are now known to result for the most part from the expansion of unstable trinucleotide repeats. This group of disorders, generally referred to as the spinocerebellar ataxias or SCAs, may now be classified with the use of a simple genetic nosology. The nosology is essentially a sequential list in which each new SCA is given a number and, in contrast to Harding's classification, the Arabic numeric system is used.

The last discovered autosomal dominant SCA is SCA type 26 [16] maps to chromosome 19p13.3, adjacent to SCA6 (see Table 1, 2).

Recent advances in the understanding of SCA pathogenesis provide the opportunity to subclassify part of the disorders based on pathogenesis: polyglutamine disorders, channelopathies, and gene expression disorders. At present such knowledge is not able to be applied from a clinical perspective. We eagerly anticipate that the meaning and value thereof will be realized in therapy specific to individual diseases or types of diseases.

### Differential Diagnosis in Spinocerebellar Ataxias

The following paper is not a description of individual clinical or molecular-genetic defined units. It is based upon the logically thought-out approach with which the neurologist works while examining the etiology of an ataxic patient (see Scheme 1). Individual comments draw attention to the stumbling blocks inherent in each and every step of the diagnostic approach and are referred to in the tables which follow.

#### Step 1 (Scheme 1):

##### Family History and Clinical Neurological Investigation

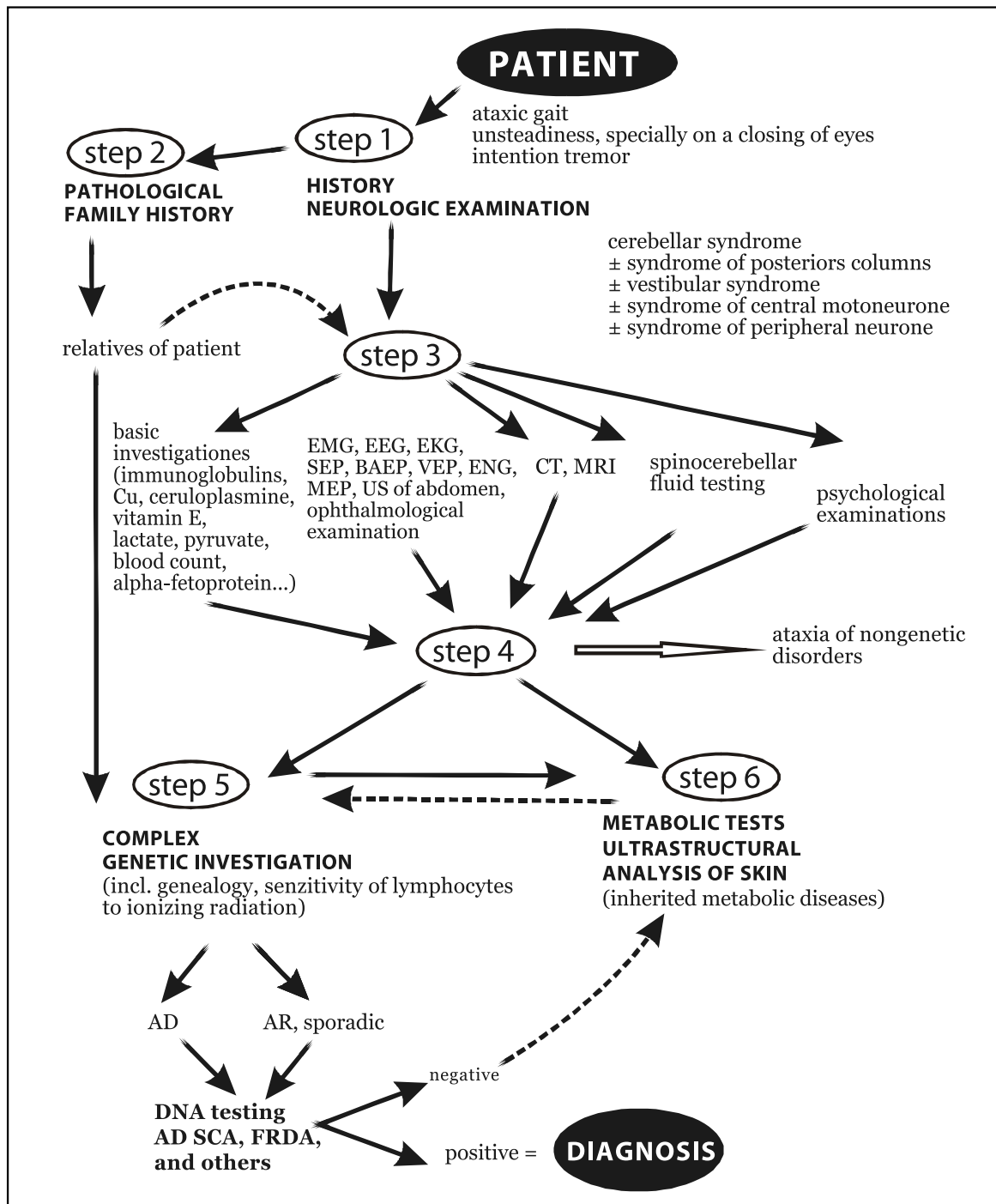
• It becomes apparent with the determination of the basis of the detraction of patient history whether sporadic or familial forms are present; sporadic and familial forms, however, are not in and of themselves indicative of the type of inheritance. Both forms may be of genetic origin. The hereditary ataxias can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. In some mitochondrial disorders [29], the maternal type of inheritance is within the realm of possibility.

Problems related to certain types of inheritance may be present in patients:

- without a full family or with an uncooperative wider family group
- with repeated diseases, in which cases anticipation occurs
- a) symptoms of earlier generations are not connected with the current problems of a particular patient
- b) illness manifests itself earlier in descendants than in their families – even in such cases as when both have the same type of mutation, albeit at a different stage of expansion
- such cases (rarely) involve the first occurrence of mutation in the family.

• The clinical manifestation of cerebellar dysfunction reflects asynergia of muscular activity. Motor disturbance involving gait, coordinated limb movements, speech, and extraocular movements dominate (see Table 3).

In the past decade, various studies suggest that the cerebellum participates not only in motor control, but also in the organizations of higher order function such as planning, setshifting, verbal fluency, abstract reason-



Scheme 1. Differential Diagnosis of Syndrome Spinocerebellar Ataxia

ing, working memory, spatial cognition and memory as well (Schmahmann and Sherman – newly defined clinical entity “The Cerebellar Cognitive Affective Syndrome”) [39].

The term ataxia is used to summarize the combined effects of movement and dysmetria. From a neurological point of view ataxia may be defined as follows:

- 1 **peripheral** (neuritic and a radicular)
- 2 **spinal** (syndrome of posteriors columns, mostly with spinocerebellar and eventually the pyramidal tracts)

3 **bulbo-ponto-peduncular** (ataxia due to altered profound sensation but also the cerebellar system, eventually vestibular system)

4 **cerebellar**

5 **cerebral**, so-called **pseudocerebellar ataxia**. (mostly a damage of frontal lobe, rarely of temporal and parietal lobe; a damage of corpus callosum means a combination ataxia and apraxia. Ataxia due to a lesion of thalamus stems from a disturbance of profound sensation.

6 **labyrinth's ataxia**

7 **functional (psychic) ataxia**

**Table 1. Autosomal dominant (spino)cerebellar ataxias (ADCA) [5,11,15,44,50,51]**

SCA	Percent of all ADCA	Average Onset (Years)	Average Duration (Years)	ATAXIA and	Genetic/ Biochemical Defects
SCA1	6% (5–27)	4th decade (<10 to >60)	15 (10–28)	Peripheral neuropathy Pyramidal signs	6p23 CAG expansion Ataxin-1
SCA2	15% (13–24)	3rd–4th decade (<10 to >60)	10 (1–30)	Abnormal ocular saccades dementia Peripheral neuropathy	12q24.1 CAG expansion Ataxin-2
SCA3	21% (11–36)	4th decade (10–70)	10 (1–20)	Pyramidal and extrapyramidal signs; lid retraction, nystagmus, decreased saccade velocity; amyotrophy sensory neuropathy	14q24.3–q32.2 CAG expansion
SCA4	Rare	4th–5th decade (19–59)	Decades	Sensory axonal neuropathy	16q22.1
SCA5	Rare	3rd–4th decade (10–68)	>25	Myokymia, nystagmus, and altered vibration sense; Early onset, slow course	11p11.q11 CAG expansion not demonstrated as yet
SCA6	15%	5th–6th decade (19–71)	>25	Slowly progressive ataxia; Sometimes episodic ataxia	19p13 CAG expansion with altered alpha1A subunit of the voltage-dependent calcium channel (CACLN1A4)
SCA7	5%	3rd–4th decade (0.5–60)	20 (1–45)	Visual loss with retinopathy	3p21.1–p12 CAG expansion Ataxin-7
SCA8	2–5%	39 (18–65)	Normal lifespan	Hyperreflexia, decreased vibration sense	13q21 CTG expansion
SCA9	Category not assigned				
SCA10	Rare	36		nystagmus, occasional seizures	22q13
SCA11	Rare	30 (15–70)	Normal lifespan	Mild disorder ataxia	15 q14–q21.3 Mutation not identified
SCA12	Rare	33 (8–55)		Pure spinocerebellar ataxia, late dementia	5q31–q33 CAG expansion Protein phosphatase
SCA13	Rare	Childhood	Unknown	Mild mental retardation, short stature	19q13.3–q13.4
SCA14	Rare	28 (12–42)	Decades (1–30)	Early axial myoclonus	19q13.4 Protein Kinase C, gamma type
SCA15	Rare	10–50	Decades	Pure ataxia, very slow progression	3pter–3p24.2
SCA16	Rare	39 (20–66)	1–40	Head tremor	8q22.1–q24.1
SCA17	Rare	6–34	>8 years	Mental deterioration	6q27 TATA-box binding protein
SCA19	Rare	34 (20–45)	Decades	Cognitive impairment, myoclonus, tremor	1p21–q21
SCA20	Rare	46 (19–64)	Decades	Early dysarthria, dystonia, dentate calcification	11cen
SCA21	Rare	6–30	Decades	Mild cognitive impairment	7p21–15
SCA22	Rare	10–46	Decades	Slowly progressive ataxia	1p21–q23
SCA23	Rare	5th–6th decade	>10 years	Late-onset ataxia and sensory loss	20p13–12.3
SCA25	Rare	1.5–39	Unknown	Sensory neuropathy	2p21–p13
DRPLA	Rare Japan – 20%	8–20 or 40–60	Early onset correlates with shorter duration	chorea, seizures, myoclonus, and dementia	12p13.31 CAG expansion Atrophin-1

ADCA – Autosomal dominant cerebellar ataxia

DRPLA – Dentatorubropallidoluysian atrophy

SCA – Spinocerebellar ataxia

**Table 2.** A comparison of classifications by Harding and by molecular testing [19]

Type ADCA by Harding's classification	ATAXIA and	Type SCA by gene	Percent of all SCA
I	± Dysarthria ± Ophthalmoplegia ± Atrophy of nervus opticus ± Dementia/mental retardation ± Extrapyramidal signs ± Amyotrophy	SCA1	5–27%
		SCA2	13–24%
		SCA3	11–36%
		SCA4	Rare
		SCA12	Rare
II	Retinopathy ± Ophthalmoplegia ± Dementia ± Extrapyramidal signs	SCA7	5–8%
III	Pure cerebellar ataxia	SCA5	Rare
		SCA6	15%
		SCA8	2–5%
		SCA11	Rare
	± Epilepsy	SCA10	Rare
	± Mental retardation	SCA13	Rare
	± Myoclonic epilepsy ± Chorea ± Dementia	DRPLA	Rare (20% Japan)


ADCA – Autosomal dominant cerebellar ataxia  
 DRPLA – Dentatorubropallidoluysian atrophy  
 SCA – Spinocerebellar ataxia

**Table 3. Neurological signs in SCA** (modified by Maříková T., Bauer P.: Spinocerebellární ataxie část II – problematika autosomálně dominantních spinocerebellárních ataxií. [(Spinocerebellar ataxias part II – problems of autosomal dominant spinocerebellar ataxias) (In Czech with English abstract)] Čes. a Slov. Neurol. Neurochir., 64/97, 2001, No. 6, p. 323-332) [32]

TYPE of SCA	1	2	3	4	5	6	7	8	10	11	12	13	DRPLA
Ataxia	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Dysmetria	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Dysarthria	+++	+++	+++	++	++	++	+++	+++	+++	+++	±	++	++
Dysphagia	++	++	++	±	±	++	++	-	-	-	-	+	+
Nystagmus	++	+	+++	-	-	++	+	++	+++	+++	-	++	-
Ophthalmo-plegia	++	++	++	±	±	±	++	-	-	-	+	-	-
Sensory loss	++	++	++	+	±	++	++	+	-	-	-	-	+
Fasciculation	++	++	++	-	-	-	±	-	-	-	-	-	-
Spasticity	++	±	++	-	-	+	++	++	-	-	-	-	-
Increased reflexes	++	+	++	-	-	-	+++	+	-	++	+++	+++	-
Decreased reflexes	+	++	++	++	-	+	-	+	-	-	-	-	-
Babinski sign	++	+	++	-	-	-	++	-	-	-	-	-	-
Amyotrophy	+	+	++	+	-	-	++	-	-	-	-	-	-
Chorea	+	+	+	-	-	-	+	-	-	-	-	-	++
Dementia or mental retardation	+	+	+	-	-	-	+	+	-	-	++	+++	++
Epileptic seizures	-	-	-	-	-	-	-	±	+	-	-	+	+
Axonal neuropathy	++	+++	++	+	-	-	+	-	-	-	-	-	-
Bladder dysfunction	++	++	++	±	±	±	++	-	-	-	-	±	-

DRPLA – Dentatorubropallidoluysian atrophy  
 SCA – Spinocerebellar ataxia

**Table 4. A FORM - Complex investigation in patients with spinocerebellar syndrome**

		NEUROGENETIC CENTRE of 2 <sup>nd</sup> Medical Faculty and Teaching Hospital Motol, Prague, Czech Republic		
<b>COMPLEX INVESTIGATION IN PATIENTS WITH SPINOCEREBELLAR SYNDROME</b>				
<b><u>Clinical examination:</u></b>				
Ataxia		yes	no	
Reflexes, especially L2-S2	increased	decreased	normal	
Positive Babinski sign		yes	no	
Alteration of sensation		yes	no	
Amyotrophy		yes	no	
Dystonia		yes	no	
Pes cavus		yes	no	
Scoliosis		yes	no	
Stigmatization, mental retardation, dementia		yes	no	
Other neurological signs:				
Ophthalmoplegia, rigidity, dysphagia, bladder dysfunction.....				
1. Sign: ..... When?..... That means in .....years of age				
More about a history:				
Hematological investigations				
Endocrinal investigations				
Acid-base balance				
Basic biochemical investigations, vitamin E, alpha-l-fetoprotein				
Immunoglobulins				
Cerebrospinal fluid – complex investigation				
<b><u>Special biochemical investigations</u></b> (in blood, ± urine, ± cerebrospinal fluid)				
Amino acids				
Organic acids				
Lactate a pyruvate				
VLCFA, phytanic acid				
Sulfatide in the urinary sediment				
Cholesterol and substance of lipids				
Purins, pyrimidines				
Ophthalmologic investigation				
Psychological tests				
Cardiologic examination, ECG, and echocardiogram				
Electro-oculography (EOG)				
Electro-nystagmography (ENG)				
EEG, EMG, VEP, BAEP, SEP, MEP,				
Complex investigation of a spinocerebral fluid				
MRI CNS (CT CNS)				
Ultrasonic investigation of an abdomen				
<b><i>Chromosomal testing</i></b>				
<b><i>Biopsy (skin, nerve, muscle, possibly liver)</i></b>				
<b><i>DNA testing: FRDA, AD SCA, FXTAS (± more in accordance with a rest of the investigations)</i></b>				
<b><i>Special enzyme assay</i></b>				

**Table 5. Hereditary metabolic/genetic disorders with ataxia** (see Notice 3) [8,17,18,20-23,28,25,43,38,48]

<b>INFANTILE HEREDITARY DISORDERS WITH ATAXIA</b>
<p>Ataxia teleangiectasia (AT)            SCA, Friedreich 's ataxia (see Table 1,2)            Disorders of amino acids or organic acids with ataxia (succinic semialdehyde dehydrogenase deficiency, disorders of GABA metabolism, L-2-hydroxyglutaric acidemia)            Juvenile GM 1 gangliosidosis            Pelizaeus-Merzbacher disease (deficiency of PANK 2)            Cockayne syndrome            Marinesco-Sjögren syndrome            Ramsay-Hunt syndrome            Late onset infantile form of neuronal ceroid-lipofuscinosis            Carbohydrate-deficient glycoprotein syndrome            Mitochondrial disorders (see Table 7)            Others (e.g. Gillespie syndrome, xeroderma pigmentosum, hereditary diseases from a range of vitamin B12, Cayman type of cerebellar ataxia, Joubert disease...)</p>
<b>CHILDHOOD AND ADOLESCENT HEREDITARY DISORDERS WITH ATAXIA</b>
<p>SCA, Friedreich 's ataxia (see Table 1,2)            Infantile-onset cerebellar ataxia (IOSCA)            Juvenile metachromatic and Krabbe leukodystrophy            Adrenoleukodystrophy            Niemann-Pick disease type C            Gaucher type III disease            Chronic GM 1 gangliosidosis, Chronic, late onset GM 2 gangliosidosis            Refsum disease            Wilson's disease            Abetalipoproteinemia (Bassen-Kornzweig disease)            Early-onset cerebellar ataxia with retained reflexes (EOCA)            Ataxia with vitamin E deficiency (AVED)            L-2-hydroxyglutaric acidemia            Others (e.g. mitochondrial disorders, late onset AT, Huntington disease, ALS...)</p>
<b>ADULT HEREDITARY METABOLIC DISORDERS WITH ATAXIA</b>
<p>SCA, Friedreich 's ataxia (see Table 1,2)            Adult adrenoleukomyeloneuropathy            Chronic adult GM 1 gangliosidosis            L-2-hydroxyglutaric acidemia            Adult metachromatic leukodystrophy            Adult Krabbe leukodystrophy            Others (e.g. FXTAS, mitochondrial disorders, late onset AT, ALS...)</p>

The clinical ataxia picture is the most distinctive and indispensable symptom during diagnosis. Such is the case as a consequence of the rich afferent and efferent of the brain and a wide range of further structures influencing the motor functions of the human body. The ataxia picture, however, serves for the most part as an orientational guide in the localization of particular lesion in the nervous system. For this reason, a combination of clinical testing, neuroimaging and electrophysiological methods provide a more precise picture of the localization and extent of damaged nerve tissue – see **Step 3** [46,47,4].

### Step 2 (Scheme 1):

In cases of positive familial history for SCA it is helpful to invite other family members – among whom neurological symptoms occur – to undergo more detailed clinical and laboratory examination. Furthermore, it is useful to recommend consultation with a geneticist in order to provide a more detailed genealogical evaluation.

*Notice 1: For example we examined SCA7 verified patient of healthy parents [3] as well as a SCA2 negative but ataxic daughter of SCA2 positive mother (unpublished).*

**Table 6. Autosomal recessive (AR) spinocerebellar ataxias [7,12,19]**

Disease	Gene/ Locus/ Product	Population Frequency	Onset (Years)	Duration (Years)	ATAXIA and Distinguishing Features
Friedrich's ataxia	<i>FXN</i> 9q13 Frataxin	1–2/50,000	1st – 2nd decade (4–40)	10 – 30	Hyporeflexia, Babinski responses, sensory loss, cardiomyopathy
Ataxia- teleangiectasia	<i>ATM</i> 11q22.3 Serine- protein kinase ATM	1/40,000 to 1/100,000	1st decade	10 – 20	Telangiectasia, cancer increased alpha- fetoprotein, chromosomal instability, immune deficiency
Ataxia with vitamin E deficiency	<i>TTPA</i> 8q13.1-q13.3 Alpha-tocopherol transfer protein	Rare	2–52 years, usually <20	Decades	Similar to Friedrech's ataxia, head titubation
Ataxia with oculomotor apraxia type 1	<i>APTX</i> 9p13.3 Aprataxin	Unknown	Childhood	Decades	Oculomotor apraxia, choreoathetosis, mild mental retardation, hypoalbuminemia
Ataxia with oculomotor apraxia type 2	<i>SETX</i> 9q34 Probable helicase senataxin	Unknown	10–22	Decades	Cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia
Infantile-onset spinocerebellar ataxia	<i>IOSCA</i> 10q24	Rare (Finland)	Infancy	Decades	Peripheral neuropathy, athetosis, deafness, optic atrophy, ophthalmoplegia
Marinesco- Sjögren	<i>MSS</i> 5q31	Rare	Infancy	Decades	Mental retardation, cataract, hypotonia, myopathy
AR spastic ataxia of Charlevoix- Saguenay	<i>SACS</i> 13q12 Sacsin	Decades	Childhood		Spasticity, peripheral neuropathy, retinal striation

**Table 7. Mitochondrial disorders with a symptom of ataxia**

	ATAXIA and			
	Polyneuropathy	Degeneration of spinal cord	Visual impairment	Epilepsy
<b>Friedreich's disease</b>	+	+	–	–
<b>X-linked sideroblastic anemia</b>	–	–	–	–
<b>MELAS</b>	–	–	+	+
<b>MERRF</b>	+	–	–	+
<b>NARP</b>	+	–	+	–
<b>SNE</b>	–	–	–	–
<b>HAM</b>	–	–	–	–

MELAS – Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke like episodes

MERRF – Myoclonic Epilepsy, Ragged Red Fibers

NARP – Neuropathy, Ataxia, Retinitis Pigmentosa

SNE – Subacute Necrotizing Encephalopathy

HAM – Hearing loss, Ataxia, Myoclonus (epilepsia partialis continua)



### Step 3 (Scheme 1):

Genetic forms of ataxia must be distinguished from the many acquired – nongenetic – causes of ataxia with the help of neuroimaging, electrophysiological, biochemical, hematological, ophthalmologic, and spinal fluid examinations [33,36].

The examination data base makes it possible to cover a high percentage of non-inherited diseases and to provide direction to further examination – particularly in cases of inherited metabolic diseases which may imitate AD SCA in the form manifested (see Table 4) [53].

Notice 2. Some degree of action tremor and motor instability may be observed in motor neuron disease (e.g. spinal muscular atrophy) or in deficit of sensation. Neurophysiological investigations are helpful to distinguish between central and peripheral damage of the nervous system. Neurophysiological investigations in a group of autosomal dominant spinocerebellar ataxias may serve as progression markers for clinical trials in the future. They are not too useful of help to direct genetic testing, especially in an early stage of the disease.

### Step 4 (Scheme 1):

The evaluation of acquired findings makes it to a large extent possible to:

- a) rule out acquired or non-inherited diseases with ataxia symptoms. In a number of such cases it is possible to intervene medically.
- *In infancy especially:* congenital ataxia (nonprogressive) ± cerebellar malformations, tumors of the cerebellum and brain stem, inflammations including abscess, vitamin deficiencies, gluten ataxia [45], ataxia due to toxic reasons.
- *In adult age especially:* alcoholism, demyelization, vascular disease, primary or metastatic tumors, or paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung, hypothyroidism, hyperparathyroidism, autoimmune diseases.
- b) indicate specialized examination (**step 6**) to rule out inherited metabolic defects which have a picture similar to spinocerebellar ataxia (see Table 5).

For example ATAXIA and:

- Decreased nerve conduction velocities (EMG); ± an increased protein in the cerebrospinal fluid, ± hepato(spleno)megaly (ultrasonic investigation), leukodystrophy (MRI) ⇒ *Suspicion of lysosomal diseases (e.g. late infantile, juvenile and adult forms of sphingolipidoses)*
- No biochemical deficits, ± CT scan and MRI with cerebellar atrophy. Giant visual evoked potentials and large somatosensory visual evoked potentials can be elicited. ⇒ *Suspicion of neuronal ceroid lipofuscinosis (NCL)*. Electron microscopic examination of skin or conjunctival biopsy shows typical

intralysosomal curvilinear inclusions. Molecular genetic testing is available.

- Elevated serum alpha-fetoprotein. Abnormality in colony survival assay, the ability of colony formation of a lymphoblastoid cell line following irradiation. Breakpoints involved in translocation at the 14q11 and 14q32 sites. ⇒ *Suspicion of ataxia-teleangiectasia (AT)*. Molecular genetic testing is performed for mutations affecting the *ATM* gene locus (11q22.3).
- Acanthocytosis on peripheral blood smears, decreased serum cholesterol, increased high-density lipoprotein cholesterol levels, low levels of LDL, VLDL, and triglyceride; retinitis pigmentosa. ⇒ *Suspicion of abetalipoproteinemia* (mutations in *MTP* gene, 4q22-q24, for microsomal triglyceride transfer protein).
- c) indicate, at best in cooperation with a geneticist (**step 5\***), DNA diagnostic methods in hereditary ataxia (currently part of AD SCA and Friedreich's ataxia /*FRDA*/) and others – see Table 1,6, and 7. DNA-based mutation analysis of CAG trinucleotide repeat length is a highly specific, diagnostic test for SCA1-3, SCA6 - 8, SCA12, SCA17, and DRPLA are available [1,2,5,6,9,13].

\* Notice 3: Steps 5 and 6 are divided only from historical point of view. Both groups of diseases differ in light of our knowledge in their genetic base and metabolic pathways.

## CONCLUSION

Neurodegenerative diseases were originally defined as progressive illnesses or, more precisely, as syndromes. Such diseases had an essentially homogenous clinical picture as well as an unclear etiology and there existed little or no possibility for causal therapeutic influence and impact. Molecular-genetic fact-finding methods contributed in a range of cases to the clarification of the etiology of suffering patients. The possibilities of genetic therapy have been intensively researched and results are anxiously expected. At the same time, several well-established existing forms of clinical classification have changed and original syndromes have been broken down into individually defined molecular sub-groups. The result is that *new* diseases have appeared. The process is far from finished and the daily quota of newly published information continues to grow. In this regard, centralized interdisciplinary cooperation among experts – neurologists, geneticists, radiologists, electrophysiologists and biochemists – has been focused on specific problems and assumes an even greater importance. Moreover, general problem orientation at the level of initial contact – among physicians, local doctors and clinical geneticists – also plays a larger role. One must keep in mind that each and every patient is unique and individual during the differentiation of diagnostic deliberation. The influence of other, as yet unknown forms of interaction may cause the picture of a given illness to differ from that of another manifestation of the same mutation. In addition, clinical manifestations of hereditary diseases

may be mitigated by other acquired diseases – with the exception of seldom considered genetic comorbidity [52,35,27,49].

The general differentially diagnostic progress outlined in the above text and analyzed in current specialized literature serves merely as a guide which may be applied while bearing in mind that *NULLA REGULA SINE EXCEPTIONE*.

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