Neurological Sciences (2019) 40:1335–1342
https://doi.org/10.1007/s10072-019-03856-w

REVIEW ARTICLE

Degenerative and acquired sporadic adult onset ataxia

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Received: 13 February 2019 / Accepted: 18 March 2019 / Published online: 29 March 2019

Abstract

The diagnosis of sporadic adult onset ataxia is a challenging task since a large collection of hereditary and non-hereditary disorders should be taken into consideration. Sporadic adult onset ataxias include degenerative non-hereditary, hereditary, and acquired ataxias. Multiple system atrophy and idiopathic late cerebellar ataxia are degenerative non-hereditary ataxias. Late-onset Friedreich's ataxia, spinocerebellar ataxia type 6 and 2, and fragile X-associated tremor/ataxia syndrome account for most sporadic hereditary ataxias. Alcoholic cerebellar degeneration, paraneoplastic and other autoimmune cerebellar degeneration, vitamin deficiencies, and toxic-induced and infectious cerebellar syndrome are the main causes of acquired cerebellar degeneration. The diagnostic approach should include a history taking, disease progression, general and neurological examination, brain MRI, and laboratory and genetic tests. Novel opportunities in massive gene sequencing will increase the likelihood to define true etiologies.

Keywords Sporadic ataxias · Paraneoplastic · Toxic · Vitamin deficiency · Multiple system atrophy

Abbreviations

ACD	Alcoholic cerebellar degeneration
ARCA1	Autosomal recessive cerebellar ataxia type 1
FXTAS	Fragile X-associated tremor/ataxia syndrome
GAD	Glutamic acid decarboxylase
GBCA	Gadolinium-based contrast agent
ILOCA	Idiopathic late-onset cerebellar ataxia
MIRAS	Mitochondrial recessive ataxia syndrome
MSA-C	Multiple system atrophy cerebellar type
PCD	Paraneoplastic cerebellar degeneration
SAOA	Sporadic adult onset ataxia
sCJD	Sporadic Creutzfeldt-Jacob disease
SCA	Spinocerebellar ataxia
SCLC	Small cell lung cancer
SREAT	Steroid-responsive encephalopathy associated with autoimmune thyroiditis
TOICS	Toxic-induced cerebellar syndrome
WE	Wernicke encephalopathy

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Introduction

Ataxia is an impairment of motor coordination and balance that is caused by a dysfunction of the cerebellum or its afferent and efferent pathways. Onset in adulthood was defined as onset after age of 20 years in earlier reports [1] but a recent study suggests a cut off of 40 years [2]. Three major groups of ataxia have to be considered: non-hereditary degenerative ataxias, hereditary ataxias that not seldom may present as sporadic cases, and acquired ataxias. Thus, the focus of this review will be on patients with sporadic progressive ataxia, starting after the age of 40 years. Reaching a diagnosis in these patients is a challenging task since a large collection of hereditary and non-hereditary conditions should be taken into consideration.

A recent study of a cohort of 80 patients with sporadic late-onset cerebellar ataxia showed that multiple system atrophy cerebellar type (MSA-C) was the most frequent form (36%), followed by acquired ataxias (18%), and by genetic ataxias (9%). Thirty-five percent of patients remained without a definite diagnosis [3].

Non-hereditary degenerative ataxias

At the beginning of the twentieth century, two different forms of adult onset degenerative non-hereditary ataxias were

recognized. The olivopontocerebellar atrophy by Dejerine and Thomas (1900) and cortical cerebellar atrophy by Marie-Foix-Alajouanine (1922). The former was described in two patients with onset between 40 and 52 years with a mixed cerebellar and parkinsonian phenotype. The postmortem examination showed atrophy of the cerebellum, most marked in the hemispheres, pontine nuclei, middle cerebellar peduncles, and inferior olives. The latter was described in four patients with onset between 40 and 78 years, clinically characterized by lower limb ataxia and relative sparing of upper limb coordination and speech. The post mortem examination showed atrophy of the cerebellum, which was more marked in the vermis than in the lateral lobes, normal pons, and atrophy of the inferior olives. This distinction, under different names, still persists today.

Multiple system atrophy

MSA is considered a disease entity defined by the presence of glial cytoplasmic inclusions (GCI) at postmortem examination. MSA can be divided in two main forms, parkinsonian and cerebellar. The estimated point prevalence is 3.4 to 4.9×10^{-5}, increasing to 7.8×10^{-5}among persons older than 40 years of age. Parkinsonian subtype is twice as prevalent as MSA-C in Caucasian population, as in North America and Europe, whereas MSA-C is more common in Japan [4]. A "probable" diagnosis of MSA-C is defined by the coexistence of cerebellar dysfunction and severe dysautonomia (systolic hypotension or urinary incontinence), whereas a "possible" diagnosis is defined by the presence of the cerebellar dysfunction and less severe dysautonomia, associated with clinical or imaging signs of dysfunction of another system (extrapyramidal or pyramidal).

In a personal series of 66 patients with probable or possible MSA-C the mean age at onset ± SD was 56.4 ± 7.3 years, the median age at wheelchair 62 (49 to 74) years, and the median age at death 63 (48 to 77; unpublished).

MRI findings showed constant cerebellar atrophy associated with pons atrophy in 76% of patients, hot bun sign in 64%, and hyperintensity of the putaminal rim in 14% (Fig. 1).

Sporadic adult onset ataxia/idiopathic late-onset cerebellar ataxia

The other form of non-hereditary degenerative ataxia is the sporadic adult onset ataxia [5] or idiopathic late-onset cerebellar ataxia [1]. The nosology of sporadic adult onset ataxia (SAOA) is ill-defined. There is no pathological hallmark. It is probably a heterogeneous syndrome, where unidentified genetic or acquired causes might contribute. Epidemiological studies are scarce and outdated. They give an estimate from 2.2 to 12.4×10^{-5}. Selection criteria are vague, tests performed variable, and populations (Caucasian or Japanese) different. Altogether, they suggest that SAOA might outnumber the hereditary forms [5]. The diagnosis of SAOA is difficult at the onset of the disease. From 5 to 24% of SAOA patients will evolve to MSA within 4–5 years [2, 6].

Onset is between 41 and 56 years [1, 2]. Time to loss of independent walking, annual increase of ataxia severity, and survival are better than MSA-C with a median survival of 21 years [5].

SAOA shows extracerebellar features, the most frequent being decreased vibration sense, urinary dysfunction not as severe as in MSA-C and spasticity. In comparison with MSA-C patients, SAOA show less frequent rigidity, hyperreflexia, and bladder dysfunction [2].

MRI shows cerebellar atrophy that may be associated with reduction in size of middle cerebellar peduncles and brainstem not as severe as in MSA-C [7].

Hereditary ataxias

It is not uncommon that a HA either autosomal recessive or dominant may present as sporadic case. Fifteen percent of FRDA patients may present with an onset ≥ 25 years, and rare FRDA patients may have an onset > 60 years. GAA expansion in the smaller allele is usually short and the phenotype might be atypical with retained knee jerks and spasticity [8]. MRI may show cervical cord atrophy, and normal/slight atrophy of the cerebellum. Mutations in the paraplegin gene, initially identified in a form of recessive spastic paraplegia, SPG7, are now recognized as one of the commonest cause of sporadic genetic ataxias with or without spasticity. Mean age at onset is in the fourth decade [9, 10]. MRI shows slight atrophy or normal cerebellum.

Mutations in *SYNE1* cause autosomal recessive cerebellar ataxia type 1 (ARCA1), where ataxia is frequently associated with upper or lower motor neuron signs. Onset usually occurs in the third or fourth decade and sometimes later. MRI shows constant and marked cerebellar atrophy. Mutations in *POLG* gene cause mitochondrial recessive ataxia syndrome (MIRAS) that may have adult onset. The disorder resembles FRDA without pyramidal signs and shows MRI findings of inconstant cerebellar atrophy and T2/Flair cerebellar and thalamus hyperintensities [11]. FXTAS is caused by a premutation (55–200 CGG repeats) in the 5′ untranslated region of *FMR1* gene. It usually occurs in men and less frequently in women. Mean onset age is 58 years. The phenotype is that of progressive cerebellar ataxia associated with tremor, parkinsonism, peripheral neuropathy, autonomic features, and cognitive decline. MRI shows T2/Flair hyperintensity lateral to dentate nucleus, of the middle cerebellar peduncle and corpus callosum, and brain atrophy in most cases [12].

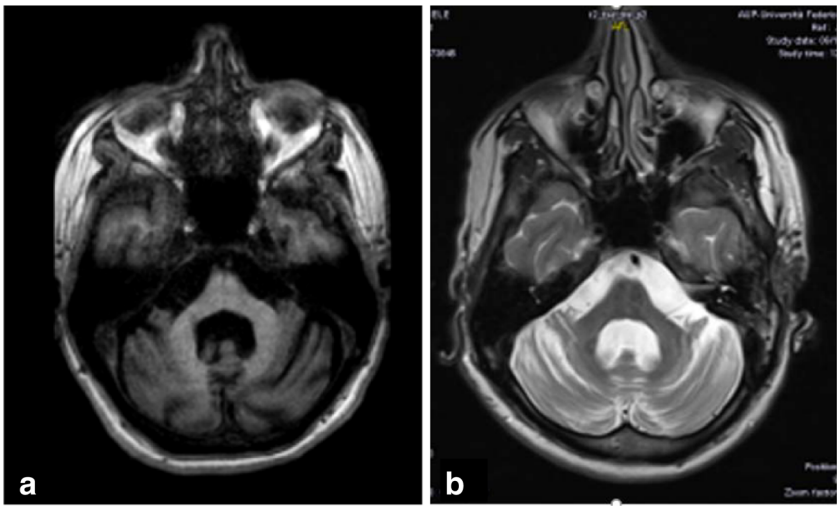

Fig. 1 MRI axial Flair-weighted sequence through middle cerebellar peduncle in a patient with MSA-C (**a**) and axial T2-weighted sequence in a patient with SCA2 (**b**). Atrophy of the cerebellum, the pons, and the middle cerebellar peduncle and enlargement of the fourth ventricle are similar

Dominant mutations may present as adult onset sporadic ataxias. De novo mutations, uncertain paternity, and early death of the parents might be responsible. Mutations in *CACNA1A* gene (SCA6) are reported as the most frequent in sporadic patients [2]. This is a pure cerebellar form and MRI shows atrophy of the cerebellum with the sparing of the pons. In our experience, pathological CAG expansions in *SCA2* were a frequent possible cause of adult onset sporadic ataxia (unpublished). It is characterized by onset in the fourth decade, slowing of saccades and a marked, early atrophy of cerebellum and pons. These MRI findings are indistinguishable from MSA-C findings (Fig. 1).

Acquired ataxias

Acquired ataxias represent a heterogeneous group of disorders including autoimmune (paraneoplastic and non-paraneoplastic), toxic, vitamin deficiencies, and infectious causes. Metabolic encephalopathies and ataxia due to focal lesions of the cerebellum such as stroke, tumor, or multiple sclerosis are not covered.

Paraneoplastic cerebellar degeneration

Cerebellar degeneration is the most common paraneoplastic neurological syndrome accounting for 40% of cases. On the other hand, antibody testing is negative in about 40% of paraneoplastic cerebellar degeneration (PCD). Almost every tumor may cause PCD, but those most commonly associated are small cell lung cancer (SCLC), cancer of the breast and ovary, and Hodgkin lymphoma. In up to 70% of cases, ataxia precedes the detection of the tumor. The pathological substrate is the loss of Purkinje cells and inferior olives not constantly associated with intraparenchymal inflammation. Typically, PCD is associated with a subacute onset and rapid progression leading to development of severe ataxia in less than 12 weeks [13]. Forty percent of the cases are asymmetric at the beginning but become symmetric in the course of the disease. There is a strong association between specific antibodies, cancer type, and neurological syndrome. A relatively pure cerebellar syndrome is associated with anti-Yo antibodies and ovarian or breast cancer, or anti-Tr antibodies and Hodgkin lymphoma. A more diffuse neurological involvement including paraneoplastic encephalomyelitis, limbic encephalitis, and peripheral sensory neuropathy is associated with SCLC and anti-Hu antibodies. Opsoclonus is associated with Ri antibodies and ovarian or breast cancer. A Lambert-Eaton myasthenic syndrome may develop in patients with SCLC and VGCC antibodies. At the beginning, MRI may be normal and a positive cortical-meningeal enhancement and a slight enlargement of the cerebellar hemispheres may be present. FDG-PET may also show increased metabolism. Cerebellar atrophy develops later on and FDG-PET shows decreased metabolism. CSF shows mild inflammatory changes with increased lymphocytes and protein and intrathecal synthesis of immunoglobulines. Antibodies associated with PCD are mainly directed against intracellular antigens (onconeuronal antibodies). The pathogenicity of these antibodies is debatable. A T cell–mediated mechanism has been proposed [14, 15].

The most frequent onconeural antibodies associated with PCD are anti-Yo (38%), anti-Hu (32%), anti-Tr (16%), and anti-Ri (12%) [14, 16] (Fig. 2 and Table 1).

Antibodies targeting cell surface antigens are less frequently associated with PCD and are considered to be directly pathogenetic. They are restricted to metabotropic glutamate receptor 1 (anti-mGluR1) and voltage-gated calcium channel (anti-VGCC). Other antibodies found in patients with PCD include

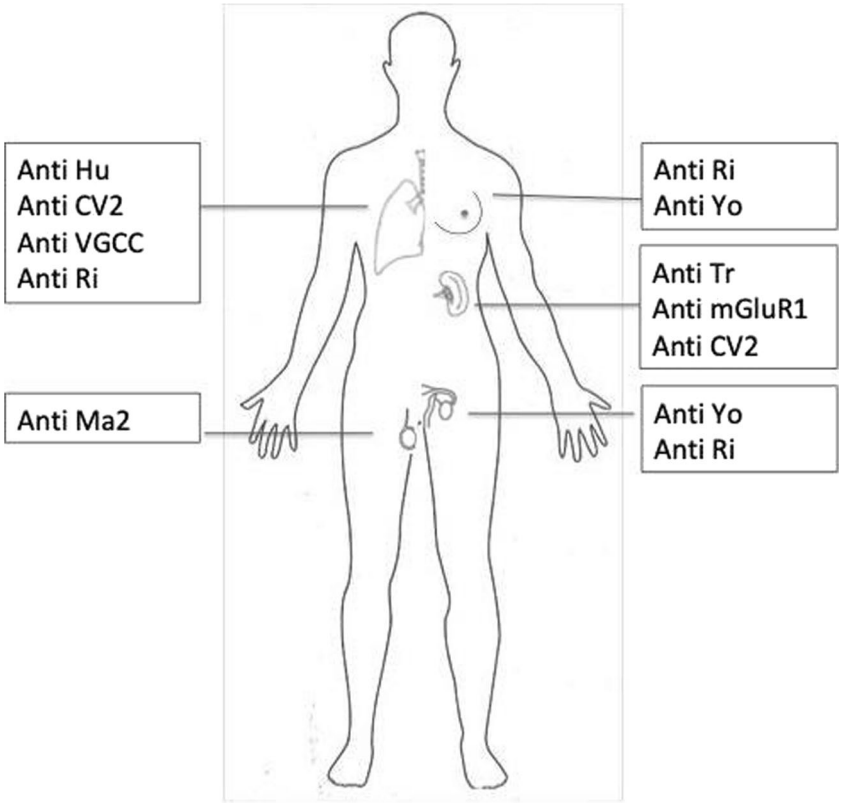

Fig. 2 The most frequent localizations of tumors that are responsible for paraneoplastic cerebellar degenerations and in the frames the related antibodies

anti-CV2/CRMP5, anti-ZYC4, anti-glycine, anti-GAD, and anti-Ma proteins.

In general, PCD does not respond to immunotherapy or tumor directed therapy. This is in agreement with an early and irreversible T cell–mediated destruction of Purkinje cells. On the contrary, PCD associated with neuronal cell surface antibodies (anti-Tr and anti-MGluR1) and Hodgkin lymphoma may improve with antitumoral therapy [17].

Survival from time at the diagnosis is worse in patients with anti-Yo (13 months) or anti-Hu (median 7 months) than in patients with anti-Tr (median 113 months) or anti-Ri (> 68 months) [15].

Tips to diagnosis are rapid development of symptoms and signs of inflammation in CSF with high IgG index and CSF-specific oligoclonal bands. Most tumors are identified by chest, abdomen, and pelvis CT or FDG-PET or both. Gonadal tumors as ovarian teratomas that do not have FDG uptake or intratubular germ cell testicular neoplasm not visible at any test pose diagnostic problems.

Table 1 The most frequent antibodies associated with paraneoplastic cerebellar degeneration and related clinical syndromes

Antibody	Syndrome
Anti-Yo	Cerebellar degeneration
Anti-Hu	Cerebellar degeneration, encephalomyelitis, limbic encephalitis, peripheral sensitive neuropathy
Anti-Tr	Cerebellar degeneration
Anti- Ri	Cerebellar degeneration, opsoclonus
Anti-VGCC*	Cerebellar degeneration, Lambert-Eaton
Anti-mGluR1*	Cerebellar degeneration
Anti-CV2/CRMP5	Cerebellar degeneration, chorea, encephalomyelitis, peripheral sensitive neuropathy
Anti-ZYC4	Cerebellar degeneration
Anti-glycine receptor	Cerebellar degeneration, progressive encephalopathy with myoclonus
Anti-GAD	Cerebellar degeneration, limbic encephalopathy, stiff person
Anti-Ma proteins*	Cerebellar degeneration, limbic encephalitis, encephalomyelitis, opsoclonus

*Antibodies to surface antigens are possibly pathogenic

Non-paraneoplastic autoimmune diseases

Coeliac disease

Coeliac disease is a systemic immunomediated disease that may affect persons of any age and many races and ethnic groups. Coeliac disease affects 0.6–15% of the population worldwide. Frequent features include chronic diarrhea, abdominal distension, weight loss, iron deficiency, aphthous stomatitis, fatigue, and reduced bone mineral density. Dermatitis herpetiformis is an unusual manifestation. Complications associated with untreated coeliac disease include neurological disorders (ataxia, peripheral neuropathy, headache, anxiety, depression, seizures), jejunum-ileitis, and cancer (T cell lymphoma and carcinoma of the jejunum). Initial testing consists in measurement of serum anti-transglutaminase IgA (sensitivity 94%, specificity 97%). Measurement of antiendomysial IgA antibody is nearly 100% specific but should be used as confirmatory test. Biopsy of the small intestine is required in most patients to confirm the diagnosis. The characteristic histologic changes include an increased number of intraepithelial lymphocytes, elongation of the crypts, and partial to total villous atrophy. Testing for HLA-DQ2 and HLA-DQ8 may be used in at-risk persons because of the high negative predictive value, which means that the disease is very unlikely to develop in persons who are negative for both HLA-DQ2 and HLA-DQ8. Treatment consists in gluten-free diet that improves the intestinal features and normalizes serum coeliac antibodies. Prognosis of neurological features is variable. Stabilization or sometimes improvement of cerebellar ataxia has been reported. The existence of a gluten ataxia that is a sporadic ataxia associated with silent coeliac disease defined by the presence of positive antigliadin antibodies, as suggested by Hadjivassiliou [18], is still debated. Indeed, positive antigliadin antibodies are found also in genetic form of ataxia as SCA2. Recently, antibodies against a novel transglutaminase isoenzyme TGM 6 were reported in patients with sporadic ataxia and asymptomatic coeliac disease [19].

Cerebellar ataxia with anti-GAD antibodies

Antibodies against the glutamic acid decarboxylase 65 are the hallmark of type 1 diabetes. They also have been reported in patients with rare neurological disorders including cerebellar ataxia, stiff person syndrome, refractory epilepsy, and limbic encephalitis. Anti-GAD antibody–related ataxia mostly affects women in the sixth decade. Clinically, it is a slowly progressive cerebellar syndrome associated with a cerebellar atrophy in about half of patients [20]. The diagnosis is made by detection of serum anti-GAD antibodies. CSF examination usually shows oligoclonal bands and intrathecal synthesis of anti-GAD antibodies with normal cellularity and proteins [21]. As far as prognosis is concerned, most patients remain disabled despite protracted immunosuppression. Intravenous immunoglobulin may have beneficial effects in some patients [22].

Cerebellar type of Hashimoto encephalitis

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a debated entity characterized by the association of neuropsychiatric signs and anti-thyroid peroxidase antibodies. Besides obligate cognitive impairment, various neurological symptoms including ataxia, tremor, and myoclonus are present [23]. A rapid clinical improvement follows steroid administration.

Toxic-induced cerebellar syndromes

Alcoholic cerebellar degeneration

Although epidemiological studies are lacking, alcoholic cerebellar degeneration (ACD) seems to be the most common acquired ataxia affecting up to 30% of all chronic alcoholic abusers.

Cerebellar ataxia usually develops slowly and is progressive. It involves mainly stance and gait, whereas ocular movements, speech, and upper limbs and coordination are relatively spared. This is in agreement with pathological findings of atrophy of anterior lobe of cerebellum (vermis mainly and adjacent hemispheres). MRI shows vermal atrophy. Cerebellar atrophy may present without ataxia in chronic alcohol abusers.

Toxic action of alcohol and acetaldehyde, together with vitamin B1 deficiency, is responsible for the loss of Purkinje cells that is associated with thinning of the granule cell layer and atrophy of the cerebellar white matter. Strict abstinence improves ataxia in alcoholics [24].

Wernicke encephalopathy

ACD is a chronic counterpart of acute vitamin B1 deficiency that causes Wernicke encephalopathy (WE). WE is characterized by confusion, oculomotor abnormalities, and ataxia. Peripheral neuropathy, hypotension, hypothermia, and seizures may be present. The pathological hallmarks are hemorrhagic lesions around the third ventricle, mammillary bodies, and thalamus. Besides alcoholism, other conditions may cause WE as bariatric and intestinal surgery, prolonged parenteral nutrition, hyperemesis, psychogenic food refusal, and chemotherapy. Treatment consists in 50–100 mg intravenously vitamin B1 followed by oral route supplementation [24].

Other forms

Different drugs may induce ataxia. The clinically most relevant include anticonvulsants (as phenytoin and carbamazepine), antineoplastics (as fluorouracil and capecitabine), psychiatric drugs (lithium), antiarrhythmics (amiodarone), anti-infective drugs (metronidazole), and drugs of abuse (cocaine, heroin, methadone, phencyclidine). Ataxia may be caused by poisoning with heavy metals (thallium, mercury, and organic lead compounds). Patients with preexisting cerebellar disease are more prone to develop ataxia. Treatment requires early withdrawal of the causative drug. Hemodialysis has been proposed as beneficial in acute lithium intoxication [24].

Vitamin deficiencies

Vitamin B12 deficiency

The most frequent cause of severe vitamin B12 deficiency is loss of intrinsic factor due to autoimmune atrophic gastritis, historically called "pernicious anemia." Other causes include gastric bypass surgery or long-term vegetarian or vegan diet. The most common neurological features are symmetrical paresthesia and gait problems. Those are related to degeneration to dorsal columns and pyramidal tracts. MRI shows characteristic hyperintensity on T2-weighted images in the cervical and thoracic cord (Fig. 3). Laboratory findings may reveal low serum vitamin B12. Since false positive or negative values are common, evidence of increased methylmalonic acid and homocysteine is relevant for diagnosis. There are many recommended schedules for treatment. Patients should receive eight to ten loading doses of intramuscular 1000 mcg vitamin B12 followed by 1000 mcg monthly. High-dose oral administration (1000–2000 mcg daily) is also effective [25].

Vitamin E deficiency

Vitamin E deficiency occurs in malabsorption (coeliac disease, cystic fibrosis, short bowel, biliary atresia, and intrahepatic cholestasis). Cerebellar atrophy develops slowly. Other features including retinitis pigmentosa may occur. Treatment consists in 800 IU vitamin E oral supplementation [26].

Infectious cerebellar diseases

Acute cerebellitis occurs more frequently in children. It occurs as primary infection or post-infectious disorder or after vaccination. In children, varicella accounts for always three-quarters of cases. In adults, Epstein-Barr virus infection or varicella reactivation is the most frequent. Chronic infections of the CNS can lead to progressive ataxia. They include tabetic neurosyphilis, Lyme Borreliosis, Whipple's disease, and the ataxic variant of sCJD. HIV-positive individuals may also show ataxia usually due to focal lesions or caused by opportunistic infections or lymphoma [27].

Superficial siderosis

Superficial siderosis is caused by deposition of pure iron or hemosiderin in the pial and subpial spaces of the brain and of the spinal cord. Causes may be acquired as vascular tumors, vascular abnormalities, subarachnoid bleeding, neurosurgical procedure, or genetic as aceruloplasminemia. Features include ataxia, hearing loss, and pyramidal signs. Diagnosis is made by linear hypointensity on T2-weighted MRI images. The therapeutic approaches consist in eliminating cause of bleeding [28].

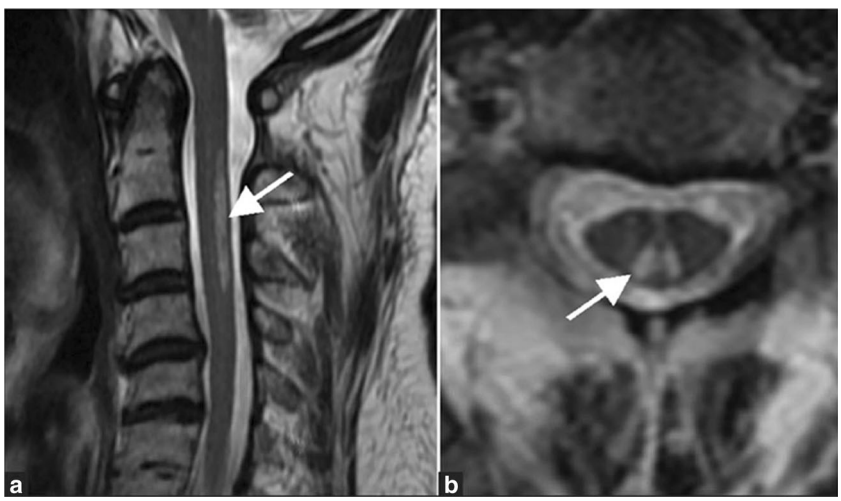

Fig. 3 **a** and **b** Cervical sagittal and axial T2-weighted sequences in a patient with vitamin B12 deficiency

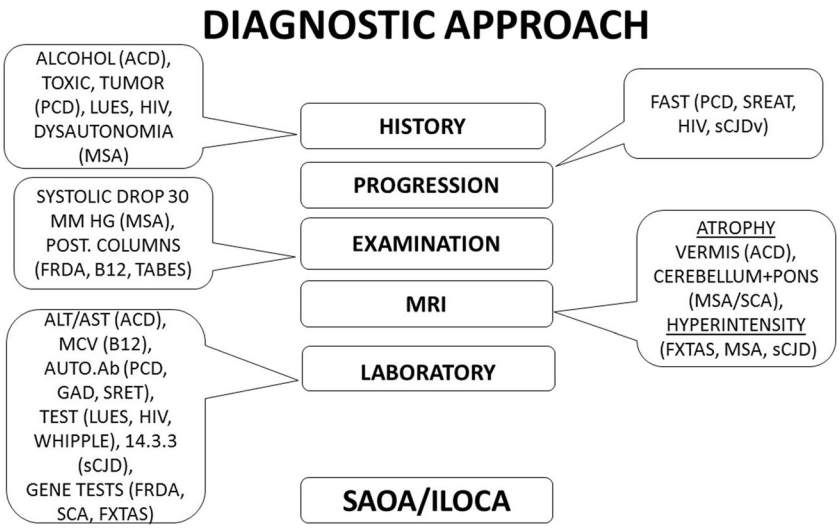

Fig. 4 Diagnostic approach. In case of a negative work out, a possible diagnosis of SAOA/ILOCA should be considered. ACD alcoholic cerebellar degeneration, FXTAS fragile X-associated tremor/ataxia syndrome, GAD glutamic acid decarboxylase, GBCA gadolinium-based contrast agent, ILOCA idiopathic late-onset cerebellar ataxia, MSA-C multiple system atrophy cerebellar type, PCD paraneoplastic cerebellar degeneration, SAOA sporadic adult onset ataxia, sCJD sporadic Creutzfeldt-Jacob disease, SCA spinocerebellar ataxia, SREAT steroid-responsive encephalopathy associated with autoimmune thyroiditis

Gadolinium deposition in the brain

T1-weighted hyperintensities in dentate and in globus pallidus are reported after repeated administration of gadolinium-based contrast agent (GBCA). This effect may be more evident with linear GBCA than with the macrocyclic. The demonstration of clinical relevant effect upon motor or cognitive function is still lacking [24].

Diagnostic approach

History taking, careful neurological examination, laboratory and genetic tests, and MRI are the pivotal points of the diagnostic pathway of the sporadic adult onset ataxia (Fig. 4).

Parental consanguinity or origin from a small isolated village suggests a genetic recessive etiology. Careful may evidence exposure to alcohol or other toxic or infectious agent. Erectile or bladder dysfunctions may orientate to a diagnosis of MSA. A history of tumor hints to a PCD. Progression is fast in PCD, SREAT, and sCJD variant. Oriented neurological examination may show a mainly posterior cordonal syndrome that hints to acquired disorders as vitamin B12 deficiency or tabetic degeneration or a genetic disorder as FRDA. A specific MRI pattern may be found in some disorders: middle cerebellar peduncles hyperintensity in MSA-C and FXTAS, pulvinar sign in sCJDs variant, atrophy of the cerebellum and pons in MSA-C and SCA2, and superior vermis atrophy in ACD. Laboratory testing is useful: abnormal liver markers in ACD, increased MCV in vitamin B12 deficiency, and detection of autoantibodies in PCD, SREAT, and anti-GAD. Test for infection diseases include syphilis, HIV, and Whipple's disease. Finally, gene tests are advisable for FRDA and SPG7 if cerebellar atrophy is not prominent, SCAs if cerebellar atrophy is present, FXTAS where onset is > 45 years, and tremor or cognitive decline and infra/supratentorial MRI hyperintensities are associated.

Even accurate screening is not able to solve all cases. Next-generation sequencing may help lead to unexpected diagnosis and may contribute to improving our understanding of these rare disorders.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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