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EFNS/ENS GUIDELINES / CME ARTICLE

EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood

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Background and objectives: The ataxias are a challenging group of neurological diseases due the aetiological heterogeneity and the complexity of the genetic subtypes. This guideline focuses on the heredodegenerative ataxias. The aim is to provide a peer-reviewed evidence-based guideline for clinical neurologists and other specialist physicians responsible for the care of patients with ataxia.

Methods: This guideline is based on systematic evaluations of the relevant literature and on three consensus meetings of the task force.

Diagnosis: If acquired causes are ruled out, and if the disease course is rather slowly progressive, a (heredo)degenerative disease is likely. A positive family history gives much guidance. In the case of a dominant family history, first line genetic screening is recommended for spinocerebellar ataxia (SCA) 1, 2, 3, 6, 7 and 17 (level B), and in Asian patients also for dentatorubral-pallidoluysian atrophy (DRPLA). In the case of recessive disease, a stepwise diagnostic work-up is recommended, including both biochemical markers and targeted genetic testing, particularly aimed at Friedreich's ataxia, ataxia telangiectasia, ataxia due to vitamin E deficiency, polymerase gamma gene (POLG gene, various mutations), autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) and ataxia with oculomotor apraxia (AOA) types 1 and 2. If family history is negative, we still advise to screen for the more common dominant and recessive ataxias. In addition, if onset is below 45 years we recommend the full work-up for recessive ataxias; if onset is above 45 years we recommend to screen for fragile X mental retardation 1 *FMR1* premutations (good practice points). In sporadic cases with an onset after 30 years, a diagnosis of multiple system atrophy should be considered (good practice point). In particular the genetic work-up will change over the upcoming years due to the diagnostic utility of new techniques such as gene panel diagnostics based on next generation sequencing for routine work-up, or even whole exome and genome sequencing for selected cases.

Treatment: Some of the rare recessive ataxias are treatable, but for most of the heredodegenerative ataxias treatment is purely symptomatic. Idebenone is not effective in Friedreich's ataxia (level A). Riluzole (level B) and amantadine (level C) might provide symptomatic relief, irrespective of exact etiology. Also, varenicline

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for SCA3 patients (level B) can be considered. There is level Class II evidence to recommend physiotherapy, and Class III data to support occupational therapy.

Introduction

The ataxias are a challenging group of diseases, particularly because of the enormous aetiological heterogeneity. This guideline focuses on the chronic, progressive (i.e. non-episodic) ataxias of cerebellar or spinal origin, and with that there is an emphasis on heredodegenerative etiologies. Acute and subacute ataxias, which most often have an acquired cause, are not discussed or only briefly mentioned. While the initial assignment was to consider ataxias with an adult onset, we have decided to cover ataxias in adulthood. The reasons are that (i) many patients first present themselves at an adult age but have had symptoms since early childhood, in which case the differential diagnosis needs also to include ataxia disorders that manifest at these earlier ages, (ii) ataxia in childhood is frequently associated with additional manifestations such as intellectual disability, shifting the focus of diagnostic work-up on the causes of cognitive dysfunction rather than on movement disorder, and (iii) the diseases that typically have an adult onset, for example most of the dominantly inherited cerebellar ataxias, have a broad age at onset range and can occasionally present in childhood.

Perhaps the most challenging category of causes is the genetic one as molecular genetic studies over the past 20 years have already identified more than 100 genes that, when mutated, lead to cerebellar ataxia. Because of this continuously expanding list of genes and further widening of the corresponding phenotypic spectra, we have tried to provide guidance on which genetic causes to consider (and how to test for them) depending on the various disease scenarios.

Method for reaching consensus

The proposal for this guideline was approved in December 2010 by the EFNS Scientific Committee. The task force has had three meetings, in March 2011, in March 2012 and in October 2012. The first meeting was used to discuss the structure and focus of the guideline, and to identify areas and issues that required literature searches according to evidence-based medicine standards. These topics were divided between the task force members; JvG was responsible for the initial searches, and search strategies and interpretation were then discussed with the respective task force member. The second meeting was used to further discuss the structure of the guideline, the diagnostic work-up, and the results of evidence-based medicine searches. BvdW and JvG then wrote a first draft with the main recommendations, and this was discussed in detail at the third meeting. Following this, other experts in the ataxia field were asked to be a part of a 'reading group' and to comment on the guideline. The guideline was finalized after this.

It will be clear that a lot of recommendations are good practice points [1]. In particular those for the diagnostic part are based on the expert opinion of this task force because of the absence of good quality studies.

Search strategy and classification of evidence

Computerized searches in the MEDLINE, EMBASE and Cochrane databases were conducted using relevant keywords for the following issues: screening for spinocerebellar ataxia (SCA) gene mutations in non-familial ataxia; screening for fragile X mental retardation 1 *FMR1* premutations in non-familial ataxia; genetic screening in early-onset ataxia; drug treatment of ataxia; and screening for and treatment of gluten ataxia. Papers published online before September 2012 were included in the search results. Reference lists of all included papers were manually reviewed by JvG for relevant citations (Data S1).

We have adopted the evidence classifications for diagnostic and therapeutic studies as laid down by the EFNS Scientific Committee [1]. However, with regard to the ('diagnostic') genetic screening studies, we had to introduce a modification, similar to that used in the EFNS guidelines on the molecular diagnosis of ataxias and spastic paraplegias [2]. As the genetic test is the gold standard itself, which cannot be tested against another method to assess diagnostic accuracy, we have let the Class II and Class III labels depend on the magnitude and characterization of the patient cohort studied. As all such studies are retrospective in nature, Class I is never reached and recommendations will not be higher than level B.

Related guidelines

National ataxia guidelines are available in Germany, the UK and the Netherlands. Also, there are some related EFNS guidelines, namely those on the molecular diagnosis of ataxias and spastic paraplegias [2], on the molecular diagnosis of mitochondrial disorders [3] and on screening for tumours in paraneoplastic disorders [4]. Finally, there is a European Molecular Genetics Quality Network (EMQN) best practice guideline dealing with the more technical aspects of molecular genetic testing in SCAs [5].

Acute and subacute ataxias

As said, we will not discuss these aetiological categories in detail. The differential diagnosis here is quite narrow [6]. For example, in the case of an acute ataxia, a stroke will be the most likely diagnosis. A vitamin B1 deficiency, particularly in the setting of an alcoholic, should also be considered. In subacute ataxias, a structural lesion should be ruled out. Other important causes are prion disease, cerebellitis, leptomeningeal metastases, paraneoplastic cerebellar degeneration or other immune mediated diseases such as steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) (formerly Hashimoto encephalopathy) and antiglutamic acid decarboxylase (anti-GAD) related ataxia. In all these patients, neuroimaging will be the common first step, which allows some of the diagnoses mentioned above to be made, suggested or excluded.

Diagnostic work-up in chronic ataxias

The early and important point for the further clinical reasoning and diagnostic work-up is the presence versus absence of a positive family history. We would like to stress the importance of investing in a comprehensive family history. The questions should not be restricted to cerebellar ataxias but also to other neurological and non-neurological problems (e.g. other movement disorders, spasticity, peripheral neuropathy, epilepsy, mental retardation, deafness, diabetes, visual disability etc.). Similarly, the further history and physical examination should also be used to identify these non-cerebellar elements, as these might allow a narrower differential diagnosis and thus a more focused work-up. We recommend an MRI brain scan as the first step in all patients with a chronic cerebellar ataxia, which will show or rule out structural and some of the other acquired causes and may also provide relevant clues for more heredodegenerative ataxias (Table S1).

Dominant family history

Autosomal dominant SCA is the most likely diagnosis in this scenario. There are over 35 genetic subtypes, however. Although there are some exceptions (Table S1), in general there is no phenotype sufficiently predictive of the underlying genotype. Based on relative frequencies, the SCAs caused by a coding CAG expansion (as a group) are the most common [SCA1, 2, 3, 6, 7, 17 and dentatorubral-pallidoluysian atrophy (DRPLA)] [7]. Of these, SCA1, 2, 3 and 6 are the most likely, SCA17 and particularly SCA7 is often accompanied by a specific phenotype, and DRPLA occurs mostly in those of Asian origin. Other SCAs are caused by expansions of non-coding expansions (SCA8, 10, 12, 31 and 36), while a third subgroup is characterized by more conventional mutations (point mutations, small insertions or deletions).

The onset age is commonly between ages 30 and 50 years but can be much earlier or later. A very early onset can be caused by a massive CAG expansion in SCA2 and SCA7, which leads to an aggressive disease course and early death [8,9]. On the other hand, a childhood onset has also been reported in SCA13 and SCA14 and here disease progression can be very slow onwards [10–12]. It is the rule rather than the exception that cerebellar ataxia is accompanied by other, so-called non-cerebellar features that include peripheral neuropathy, spasticity, parkinsonism, chorea, dystonia, myoclonus, dementia, ophthalmoplegia, hearing loss, intellectual impairment etc. Occasionally, these non-cerebellar features pre-date the onset of ataxia and remain to be more prominent than the cerebellar signs.

There are some other dominantly inherited disorders that have cerebellar ataxia as one of the features [13] such as neuroferritinopathy, optic atrophy 1 (OPA1), hereditary prion disease, Alexander disease, adult-onset leukodystrophy and spastic ataxia 1 (SPAX1). Typical MRI abnormalities are often the tell-tale sign, e.g. brain iron accumulation in neuroferritinopathy, and ataxia is usually not the dominant disease feature. In addition, the episodic ataxias are also dominantly inherited but the paroxysmal nature clearly contrasts the chronic progressive course of the SCAs, although we appreciate that in later disease stages a chronic progressive ataxia can develop in some of these.

With regard to genetic testing, this can be performed in three distinct situations all including an informed and written consent: (i) molecular confirmation of the disease in an affected person, allowing an already clear clinical diagnosis to be established; (ii) revelation of the presence or the absence of the muta-

tion in an at-risk person; and (iii) pre-natal and pre-implantation diagnosis for couples where one partner is a carrier or at risk for SCA. Predictive testing in an at-risk person allows an unaffected individual to know if he/she is a carrier or not. If preventive and curative treatment were available, testing could be the ideal situation. Unfortunately, to date the possibilities of prevention and treatment are not good enough to counsel in favour of genetic testing. This means that the discussions and decision making in favour or against testing will be organized according to individual needs. International guidelines were provided to give a structured predictive testing procedure. This includes pre-test counselling and interviews as well as post-test follow-ups [14].

Recommendations

- In the case of a family history that is compatible with an autosomal dominant cerebellar ataxia, screening for SCA1, 2, 3, 6, 7 and 17 is recommended (level B) [2]. In Asian patients, DRPLA should also be tested for.
- If mutation analysis is negative, we recommend contact with or a referral to a specialized clinic for reviewing the clinical phenotype and further genetic testing (good practice point).

Recessive family history

An autosomal recessive ataxia should be suspected in particular in the case of affected siblings (with healthy parents) and/or consanguinity in the family. However, family history might also be totally blank. The old rule of thumb that recessive ataxias are complex multisystem disorders that start before age 25 years is no longer valid. Some of the more classic recessive ataxias, such as Friedreich ataxia and cerebrotendinous xanthomatosis, can start very late, even after age 50 years (Table S2). In addition, some of the more recent recessive ataxia genes, like *Anoctamin 10* (*ANO10*) mutations, can give rise to a rather pure cerebellar syndrome that starts after age 40 years.

In the case of a suspected recessive ataxia, non-cerebellar features might help to make a focused differential diagnosis and prioritize diagnostic work-up. For example, if cerebellar ataxia is combined with marked spasticity, one should first consider autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) and spastic paraplegia 7 (SPG7), and if there is concomitant chorea plus a severe disturbance of saccades, disorders like ataxia telangiectasia or ataxia with oculomotor apraxia type 2 (AOA2) need to be tested for first.

In Europe and the USA, Friedreich's ataxia is the most common recessive ataxia, unlike in Japan where ataxia with oculomotor apraxia type 1 (AOA1) is the most common. The second most frequent recessive ataxia globally is ataxia telangiectasia, with the exception of North Africa where this is ataxia with vitamin E deficiency [15,16].

We have found no studies that provided a yield of a certain genetic and biochemical screening strategy. Invariably, such studies have been done in cohorts based on phenotypic selection. Therefore the recommendations below are based on expert opinion.

Recommendations

In the case of a family history compatible with an autosomal recessive cerebellar ataxia, we recommend a three-step diagnostic approach.

- Step 1: mutation analysis of the *FRDA* gene for Friedreich's ataxia (although one can refrain from this in the case of severe cerebellar atrophy), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, creatine kinase (CK) and α-fetoprotein. Also consider doing nerve conduction studies/EMG (presence versus absence of peripheral neuropathy, axonal versus demyelinating) and referral to an ophthalmologist (retinitis pigmentosa, cataract, cherry red spot etc.) (Table S2) (good practice point).
- Step 2: mutation analysis of the *SACS*, *POLG*, Aprataxin (*APTX)* and *SPG7* genes (taking into account specific phenotypes, as given in Table S2), and biochemical testing for white cell enzymes, phytanic acid and long chain fatty acids (good practice point).
- Step 3: referral to a specialized centre, e.g. for skin or muscle biopsy targeted at diagnoses such as Niemann–Pick type C, recessive ataxia with coenzyme Q deficiency [aarF domain containing kinase 3 (ADCK3)/autosomal recessive spinocerebellar ataxia 9 (SCAR9)] and mitochondrial disorders, or for extended genetic screening using gene panel diagnostics (good practice point).

Positive family history otherwise

For the work-up in the case of a family history that is best compatible with a mitochondrial disease, we refer to the EFNS guidelines on the molecular diagnosis of mitochondrial disorders [3].

In patients with a family history that reveals for example a grandchild or nephew with fragile X syndrome or a daughter with premature ovarian failure, the *FMR1* gene should be tested for CCG repeat premutations because of the so-called fragile X-associated tremor ataxia syndrome (FXTAS, see below) [17]. But

even in patients without a suspicious family history, FXTAS can be found [18]. Onset age is invariably above age 45 years.

Negative family history

In sporadic cases, it is very relevant to search for clues from the history and clinical examination. For example, in the case of clear autonomic dysfunction combined with cerebellar ataxia, a diagnosis of multiple system atrophy (MSA) should be considered at the early stage, and not all of the testing suggested below is necessary. If there are no such clues that allow you to 'jump' to a focused differential, it is important to consider and rule out acquired causes. After initial neuroimaging (see above), a limited number of blood tests can rule out some of the non-structural acquired causes, such as vitamin deficiencies, hypo(para)thyroidism and immune-mediated ataxias. These include testing for vitamins E, B1 and B12, thyroid-stimulating hormone, calcium, phosphate and anti-GAD antibodies (good practice point). Anti-GAD ataxia can have both a subacute and insidious onset [19–21]. A lumbar puncture can be considered to find supportive evidence of an inflammatory origin, such as primary progressive multiple sclerosis, and a lumbar puncture is also recommended in patients with high anti-GAD antibody titres in serum to demonstrate the actual intrathecal synthesis of GAD antibodies. If negative in cerebrospinal fluid, the anti-GAD antibodies are more likely to be related to other autoimmune (endocrine) syndromes associated with GAD antibodies, like type 1 diabetes, and unlikely to be the cause of the cerebellar ataxia [20].

Alcoholic cerebellar degeneration (ACD) is a known complication of chronic alcohol abuse. There are no data, however, that tell us how much alcohol for how long is required to develop ACD. Circumstantial evidence might come from the presence of abnormal liver function and concomitant peripheral neuropathy, but in case of doubt one should consider completing the diagnostic work-up as laid down in this section.

There is an ongoing debate on the existence of the entity referred to as gluten ataxia, which is an otherwise unexplained, slowly progressive ataxia associated with celiac-related antibodies (anti-gliadin, anti-endomysium, anti-tissue transglutaminase, anti-transglutaminase-6). Bowel symptoms are usually absent and intestinal biopsies are often normal [22]; i.e. there is no formal diagnosis of celiac disease, and the term gluten sensitivity is used. The controversy is caused by the finding of such antibodies in patients with ataxia due to a proven genetic cause [23,24],which has led to the hypothesis that these antibodies are epiphenomena, secondary to a primary degenerative process. We have reviewed 10 studies that addressed the question of prevalence and specificity of these antibodies in patients with ataxia [22–31]. Two studies were Class II [23,25] and the other eight Class III or IV [22,24,26–30]. Most studies have focused on anti-gliadin antibodies, and the combined results indicate that these antibodies are present in 9%–41% of patients with 'sporadic' ataxia, in 2%–43% of patients with a proven genetic ataxia and in 1%–12% of healthy controls. A recent study found transglutaminase 6 antibodies (TG6) in 73% of patients with gluten ataxia and in 32% of patients with sporadic ataxia. The definition of gluten ataxia was based on the presence of other celiac-related antibodies [31]. The high percentage of TG6 antibodies found in patients with gluten ataxia might just be due to the fact that they are part of the same immunological response as the other celiac-related antibodies. These data argue against a high specificity of these antibodies. The claimed potential relevance of diagnosing gluten ataxia is treatability. We have reviewed 13 studies that used a gluten-free diet, intravenous immunoglobulins or a combination thereof [26,32–43]. Except for one [37], which was Class III, all studies were Class IV studies. We therefore concluded that there is insufficient evidence to support such treatment of this already disputed entity of gluten ataxia.

Recommendation

- The task force recommends considering and ruling out acquired causes of ataxia via brain imaging and a limited number of blood tests, and considering the possibility of MSA in those with an onset over 30 years (for the revised MSA criteria see [44]) (good practice point).
- The task force does not recommend routine testing for gluten sensitivity in isolated and otherwise unexplained cases of cerebellar ataxia (level B).

Genetic testing is recommended in isolated patients, particularly if acquired causes are excluded or deemed unlikely. Several studies have revealed a genetic basis in such apparently 'sporadic' cases. Autosomal recessive or X-linked traits are not necessarily exposed through family history, and dominantly inherited ataxias can be missed due for example to reduced penetrance or death of gene carriers before onset of symptoms. We have reviewed 38 studies that partly focused on genetic testing in apparently sporadic ataxia. In total, 5569 patients were tested (Data S1). Most studies were performed in Europe or Asia, which showed regional differences. In Europe SCA6 (0.45%), SCA2 (0.31%) and Friedreich ataxia

(0.42%) were most frequently found. In Asia, the relative frequencies were SCA1 (0.52%), SCA2 (0.97%), SCA3 (3.74%), SCA6 (4.58%) and DRPLA (0.97%). However, each study used a different battery of genetic tests and different criteria for testing. Two clinical studies included only patients in whom acquired forms of ataxia had been excluded [45,46]. In these studies, both Friedreich ataxia and SCA6 were diagnosed in approximately 5% of the patients; in 1%–2% of the patients SCA2 or SCA3 was found. Further clinical evaluation revealed that 16%−29% of the patients fulfilled the criteria of possible or probable MSA. But in many studies inclusion criteria are not clearly defined. From these studies it is therefore difficult to derive a rational strategy on how to select appropriate genetic tests in isolated ataxia patients. On the other hand, with the broadening of phenotypic spectra that has emerged over the years, a routine battery of tests is likely to have a higher yield than the approach of focusing genetic testing on specific phenotypes. We have also learned that many of the recessive ataxias can have a later onset than previously assumed (Table S2), and we therefore also incorporated a more active search for recessive ataxias other than Friedreich ataxia in our recommendations.

The fragile X tremor/ataxia syndrome (FXTAS) refers to a neurological syndrome including ataxia that develops particularly in men who carry premutations in the *FMR1* gene (55–200 CGG repeats). In addition to ataxia, other features like parkinsonism, action tremor, peripheral neuropathy, autonomic disturbances, behavioural and cognitive changes can be present. In women with FXTAS, action tremor can be absent, while the features of parkinsonism are more pronounced. MRI can show hyperintensities of the medial cerebellar peduncle and within the corpus callosum [47]. We have reviewed eight studies that sought to address the frequency of the *FMR1* premutation in patients with unexplained ataxia [48–55]. In a recent study of 22 patients with FXTAS, 43% had a negative family history [18]. Three studies were Class II [49,51,55] and the other five Class III [48,50,52–54]. Most studies included only male patients with late-onset ataxia. The yield varied from 0% to 5%. All premutation carriers had an onset of ataxia after age 45 years. One recent review also looked at the combined data, and found a premutation in 1.5% of cases in men and 0.2% in women [17].

Recommendations

- In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA6 and DRPLA (in Asian patients) (level B), the step 1 panel of the recessive ataxia work-up, i.e. mutation analysis of the *FRDA* gene (level B), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, CK and α-fetoprotein.
- If negative and if age at onset is below 45 years, we recommend the full work-up for recessive ataxias (see above), for which referral to a specialized centre needs to be considered (good practice point).
- If negative and if age at onset is above 45 years, we recommend screening for the *FMR1* permutation in male patients (level B).

We have to keep in mind that the finding of a gene mutation in an isolated case is a difficult counselling issue because the sudden discovery of a hereditary disease is frightening. However, the absence of a positive family history with no known cases in the elder generations is often due to censored family histories, such as early death, adoption or false paternity. The discovery of the mutation in apparently isolated cases has important consequences for all family members since they were not aware of an inherited disorder until the genetic testing. This has to be taken into account and explained to the patient and to his/her relatives before blood sampling and testing.

Despite a full diagnostic work-up, many patients are left without a clear aetiological diagnosis. This group can be referred to as sporadic ataxias of unknown aetiology. In theory, in those with a relatively early onset a recessive disorder remains a likely scenario, while in those with late-onset disease we really do not know. It is likely that in the following years the percentage of cases with an unknown aetiology will reduce in parallel with the further implementation of more advanced genetic diagnostic techniques (see below). Clinical follow-up of such patients is required in order to see whether the disease course and/or the development of new clinical signs allow a more precise diagnosis, and to be able to subject the patient to new (genetic) tests that come available.

Near-future diagnostic developments

Due to their great genetic heterogeneity and the limited clinical specificity of different ataxia subtypes, classical diagnostic sequencing approaches are far from being time and cost efficient enough to be offered on a routine basis. Thus, clear mutation frequencies are not available yet for different populations and for larger patient cohorts. In several specialized molecular genetics laboratories gene panel targeted (or even whole exome) next generation sequencing technologies are being routinely performed allowing time and cost efficient testing of the majority of underlying genes in parallel (for instance more

than 120 genes causing ataxias or more than 60 genes causing paraplegias). These approaches will clearly broaden our understanding on the phenotype of the respective disease and will reveal the rare forms of treatable ataxias. Today, however, there are still several limitations of the technology: (i) repeat expansions are not detected by this method (thus, as stated above, they will need to be tested first); (ii) deletions and duplications are not easily detected and will need other technologies such as multiplex ligation-dependent probe amplification (for instance, SCA15 due to deletions of the inositol-triphosphate receptor type 1 gene will be missed); (iii) despite targeted-enriched exon selection, not all gene regions are satisfactorily covered which may mask mutations; (iv) due to limitations of the current databases, not all missense variations found can be clearly identified as disease causative warranting further family analysis; and (v) more than one genetic alteration may be detected opening up the question of (a) digenic inheritance, (b) difficulties in genetic counselling, (c) increasing the risk for offspring of affected individuals and thus (d) suggesting additional genetic testing of the respective partner; finally (vi) gene panels are not easily adapted to the discovery of novel genes leading to different panel compositions and versions among the different laboratories. Despite these limitations, using gene panel diagnostics it is expected that the detection rate of genetic causes in ataxias of below 50% will be dramatically increased to more than 80% in the next few years.

Management of chronic cerebellar ataxias

For some of the acquired ataxias, treatment of the underlying cause is possible. Examples thereof include vitamin B1 supplementation or surgical removal of a posterior fossa mass lesion. For most of the heredodegenerative ataxias, treatment is purely symptomatic and supportive. We will not specifically address treatment in MSA which is discussed in detail in recent reviews [56–58].

Drug treatment

A few of the recessive ataxias are treatable, and an adequate diagnosis in this category is also very relevant. These include the following.

Ataxia with vitamin E deficiency (AVED): AVED should be treated with lifelong oral administration of high-dose vitamin E. A dosage of 800–1500 mg a day is advised. Currently two different vitamin E preparations are used: *all-rac*-α-tocopherol acetate (chemical form) and *RRR*-α-tocopherol (natural form). If the treatment is started early in the disease some symptoms, like ataxia, can be stopped or reversed (Class III) [59–62].

Cerebrotendinous xanthomatosis (CTX): Chenodeoxycholic acid, which normalizes bile acid synthesis and suppresses the cholestanol biosynthesis, stabilizes clinical signs of neuropathy in a dosage of 750 mg/day [63]. HMG-CoA reductase inhibitors are also effective in improving clinical signs by reducing the cholestanol concentration (two Class III studies), but caution is required because they may induce muscle damage and in some cases even rhabdomyolysis [64,65].

Niemann–Pick type C: Miglustat is a small amino sugar molecule that inhibits glycosphingolipid (GSL) synthesis. It reduces GSL accumulation in the brain and improves some clinical symptoms, like dysphagia, but the current data in terms of significant functional benefit are not too convincing yet. The recommended dose is 200 mg three times a day (all Class III) [66–69].

Abetalipoproteinaemia: In abetalipoproteinaemia absorption of fats and fat-soluble vitamins is compromised. Early treatment with 150 mg of α-tocopherol per kilogram and vitamin A can reduce symptoms like retinopathy and neuropathy (Class IV) [70,71]. Also, a diet with reduced fat intake should be installed [72].

Refsum disease: Patients with Refsum disease need a lifelong dietary restriction of phytanic acid combined with a high-calorie diet [73]. Plasmapheresis or lipid apheresis can reduce the plasma concentration of phytanic acid by 50%–70% and relieve symptoms like neuropathy and ataxia (Class IV) [74].

Recessive ataxia with coenzyme Q deficiency (ADCK3/SCAR9): In these patients, muscle biopsy shows decreased levels of ubiquinone. Results of treatment with CoQ10, however, vary: some patients reported improvement and stabilization of ataxia, while others did not significantly improve after treatment. Reported doses ranged from 60 to 700 mg/day (Class IV) [75–77].

Recommendations

- AVED should be treated with lifelong oral administration of high-dose vitamin E (good practice point).
- Miglustat improves some clinical symptoms in Niemann–Pick type C (level B).
- Chenodeoxycholic acid stabilizes clinical signs of neuropathy in CTX (level C).
- In patients with Refsum's disease, a lifelong dietary restriction of phytanic acid and a high-calorie diet is advised (good practice point).

- In patients with abetalipoproteinaemia, a diet with reduced fat intake and treatment with α-tocopherol and vitamin A should be started (good practice point).
- In patients with recessive ataxia with coenzyme Q deficiency, treatment with vitamin Q10 should be considered (good practice point).

In addition, for the other genetic and degenerative ataxias, some drugs can provide some symptomatic relief. For a recent extensive review, see the paper by Trujillo and colleagues [78]. Drugs that showed an effect on ataxia severity are discussed in more detail.

Riluzole

Riluzole opens small-conductance calcium-activated potassium channels that have an important regulatory effect on the firing rate of neurons in deep cerebellar nuclei, thereby reducing neuronal hyperexcitability. In a double-blind placebo-controlled pilot trial including 40 patients with ataxia of different aetiologies riluzole 100 mg/day showed a mean decrease of 7 of 100 points on the International Cooperative Ataxia Rating Scale (ICARS) after 8 weeks (Class II). The cut-off for clinically relevant difference was set at 5 points [79].

Varenicline

The efficacy of varenicline, a partial agonist at α4β2 neuronal nicotinic acetylcholine receptors, in a dosage of 1 mg twice a day has been suggested in several case reports and a randomized controlled trial with SCA3 patients, in which mainly gait and stance improved (Class II) [80–83].

Amantadine

Amantadine, which has a positive effect on some parkinsonian features because it is a non-competitive *N*-methyl-D-aspartate antagonist, also has a beneficial effect in degenerative ataxias. It has been studied in patients with 'degenerative cerebellar ataxia' and Friedreich ataxia. In patients with degenerative cerebellar ataxia a sustained improvement of functional capacity on the functional ataxia scoring scale was seen with continued administration of maximal 300 mg/day (Class III and IV) [84,85] but no significant improvement was found in patients with Friedreich ataxia (Class II) [86].

Idebenone

The effect of idebenone has been studied in patients with Friedreich ataxia. A recent Cochrane review found only one well-conducted double-blind randomized controlled trial in which idebenone 5 mg/kg was compared with placebo. No significant improvement of ataxia was found. A significant decrease of left ventricular heart mass was found, but the clinical relevance of this finding is unknown. So, there is no substantial evidence to recommend idebenone as treatment for Friedreich ataxia (Class I) [87,88].

Recommendations

- Riluzole is probably effective in reducing ataxia symptoms (level B).
- Varenicline is probably effective in improving gait and stance in SCA3 patients (level B).
- Idebenone is established as ineffective in Friedreich ataxia (level A).
- Amantadine improves symptoms of functional disability in patients with degenerative cerebellar ataxia (level C).
- The task force recommends not to routinely use the other drugs because of inconsistent results or premature data (Data S2).

Although the formal interpretation of the available literature culminates in these recommendations, some results need to be confirmed. In particular, the task force considers the results for riluzole and varenicline to be preliminary but is aware of larger trials that are under way.

Allied healthcare interventions

A recent systematic review of the effectiveness of allied healthcare interventions in degenerative cerebellar ataxias concluded that there is Class II evidence for an effect of physiotherapy, Class III evidence for occupational therapy and insufficient data to comment on the effect of speech/language therapy [89]. The latter, however, is considered a good practice point by the task force in the case of clear dysarthria and/or dysphagia. Also, consulting a neurorehabilitation specialist needs to be considered, who for example can decide on the necessity of an inpatient rehabilitation programme, coordinate the allied healthcare interventions and evaluate the potential benefit of proper footwear, walking devices etc. (good practice point). Also, interacting with palliative care physicians, particularly in the later disease stages, is recommended.

Recommendations

- Patients should be referred for physiotherapy (level B).
- Referral to occupational therapy (level C) needs to be considered.

Relevant web links

http://neuromuscular.wustl.edu/ataxia/aindex.html
http://www.ncbi.nlm.nih.gov/books/NBK1116/
http://www.ncbi.nlm.nih.gov/omim/

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Searches.
Data S2. Other anti-ataxia drugs that have been reviewed by the task force.
Table S1. Dominant spinocerebellar ataxia (SCA) subtypes.
Table S2. Recessive ataxias.

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