Recent advances in the management of choreas

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Ther Adv Neurol Disord
(2013) 6(2) 117–127
DOI: 10.1177/1756285612471700

Abstract: The management of patients with chorea, in particular Huntington's disease, is a complex task requiring skills in a number of areas. This paper reviews new knowledge on this topic and places it in the context of established procedures. It is focused on Huntington's disease, since this is the disorder, for which most publications on management have been published in the past few years. Management starts with appropriate diagnosis and differential diagnosis, with the aim of finding disorders with chorea amenable to causative treatment. The place of genetic testing and the importance of genetic counselling is stressed, as well as the importance of precise observation in the course of the disorder to tailor appropriate therapies. Pharmacological treatment is based on poor evidence but to a large extent on expertise from centres devoted to the care of patients with Huntington's disease. It is focused mainly on motor and psychiatric aspects of the phenotype. Nonpharmacological treatment is important and is best offered in a multidisciplinary care setting.

Keywords: Chorea, Huntington's disease, diagnosis, treatment, management

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Introduction

Chorea, derived from the Greek word *choreia*, describes a dance-like complex characterized by involuntary, rapid, irregular, jerky, nonrepetitive movements, which are randomly distributed. They can affect all parts of the body, are typically fluctuating and their intensity is modulated by a number of internal and external factors. This is the most obvious aspect of a number of disorders usually presenting with additional features including cognitive and psychiatric abnormalities. The most frequent hereditary etiology is Huntington's disease (HD), but there are numerous other causes for chorea, including L-dopa-induced chorea in Parkinson's disease, tardive dyskinesia, metabolic, toxic and autoimmune disorders. It is important to proceed to a precise diagnostic work-up in order to search for a potentially treatable aetiology and to delineate the problems that can be addressed by symptomatic therapies. Management of these disorders involves a strongly interconnected multidisciplinary team, with the participation of different specialists during the course of the disorder, which can last for decades of chronic progression.

Diagnostic work-up

Taking a careful history will often allow the recognition of the cause of the choreatic disorder [Wild and Tabrizi, 2007a]. Information about onset, course, additional features, including other neurological features, as well as cognitive and psychiatric symptoms, will help to characterize the syndrome. Taking a general history will help to explore possible causes including drugs, metabolic disturbances, and exposure to infectious and toxic agents. Recording a detailed family history over several generations paying particular attention to consanguinity is important, however, pitfalls must be kept in mind, including nonpaternity and secrecy of disease involvement for psychosocial or other reasons. It is also important to get history information from family members and carers, since often the movement disorder is felt in quite different ways than what is observed objectively, and also because of the lack of insight in some behaviour symptoms or because of memory loss when there is cognitive involvement.

The examination will have the purpose of confirming the presence and characterization of the movement disorder as chorea, including patterns of distribution and severity. It will also be important to recognize other movement disorders, including ataxia, dystonia, myoclonus, bradykinesia and tremor. A general neurological examination will help to disclose additional features including abnormal eye movements, pyramidal and neuromuscular involvement.

In the presence of an autosomal dominant inheritance of a subtle onset and gradually progressive syndrome including chorea, cognitive and behavioural changes, which can present in a variable fashion even among members of the same family, the diagnosis of HD is the most probable. In such a case there is no need for any additional investigation and a genetic test may be contemplated, especially if this has not yet been done in another member of the family [Harbo *et al.* 2009]. This has to be performed with great care during a genetic counselling workout including the family, since such a result has important implications for the patient and their relatives, and thoughtful consideration of the information provided and the way it is received is mandatory. Furthermore, it is important to ensure that the laboratory applies appropriate quality controls, which have been recently updated [Losekoot *et al.* 2012]. In the case of a negative test, which is a rare occurrence with this typical presentation, at least in Western populations [Wild and Tabrizi, 2007b], additional information may guide further diagnosis (Table 1). Huntington-like disease 2 (HDL2) has quite a similar presentation but is found almost exclusively in people of African origin [Margolis *et al.* 2004]. Dentato-rubro-pallido-luysian atrophy (DRPLA) [Wardle *et al.* 2009] is a similar disorder found mainly in Japanese. Some of the autosomal dominant cerebrospinal atrophies, specifically SCA17 [Schneider *et al.* 2006], and more rarely others [Martino *et al.* 2012], may present with a predominant chorea. Patients with chorea acanthocytosis often have a facio-bucco-linguo-masticatory predominance of their movement disorders, with typical self-mutilation. Areflexia, weakness and muscle wasting are further hints towards this diagnosis [Jung *et al.* 2011]. Acanthocytes are typically present in blood smears, but it is important to note that specific technical considerations to detect them are needed.

It is always important to search for Wilson's disease, as this diagnosis opens up therapeutic options. Chorea, among other neurological symptoms and signs, together with liver disease and Kayser–Fleischer rings, are typical of the disorder, which can be confirmed by low ceruloplasmin and elevated urine and hepatic copper [Rosencrantz and Schilsky, 2011]. Benign hereditary chorea is a rare disorder with childhood onset of chorea, without progression, or even with a tendency to improve in adulthood, which is autosomal dominantly inherited. The recent discovery of mutations in NKX2-1 (previously named TITF1) has lead to a better understanding of the disorder [Gras *et al.* 2012] and also allows a molecular-genetic diagnosis if needed. It should be noted, however, that such mutations are only rarely found in sporadic cases [Bauer *et al.* 2006]. Paroxysmal exercise-induced dyskinesia is characterized by short episodes of dyskinesia including chorea after movement, which can recur several times a day. Thanks to novel technological approaches, the gene mutated in this disorder has recently been discovered [Chen *et al.* 2011], many years after the description of the disease locus [Tomita *et al.* 1999].

Many of the sporadic disorders with chorea may be diagnosed by taking a precise history and performing some simple laboratory tests. They include a blood count, a smear for acanthocytes, a sedimentation rate, a metabolic panel, ceruloplasmin and creatine phosphokinase levels, thyroid parameters, B12 levels and autoantibodies (antinuclear, lupus anticoagulant, anticardiolipin, antistreptolysin and anti-DNase-B) [Cardoso *et al.* 2006]. Imaging studies may be needed, they are mandatory in all cases with one-sided involvement.

Presymptomatic genetic testing

Genetic testing, specifically in HD, where confirmation of carrier status in an as-yet healthy individual has profound implications for psychological well-being and life planning, has to be performed in a careful way [Tibben, 2007]. Earlier guidelines, formulated shortly after the discovery of the gene with mutations causing the disorder, have recently been revised, although the basic assumptions and procedure guidelines remain similar [Macleod *et al.* 2012] and have been used for numerous other neurogenetic disorders [Burgunder *et al.* 2010; Harbo *et al.* 2009]. High-quality information provided in understandable words adapted to the counselee is very important. Most often, he comes with personal experience of interacting with affected people in his family and has searched for information in material provided by patients' organization and through the Internet. However, he needs to relate this information in a rational way to his present situation contemplating genetic testing, and sometimes misconceptions and wrong information has to be corrected. The first counselling sessions will also help to assess the psychological needs of the counselee and to address the appropriateness of psychological

Table 1. Major diagnostic features in hereditary disorders with prominent chorea.

Inheritance	Disease	Onset course	Additional neuro-psychiatric involvement	Other systems	Gene	Diagnostic test
Autosomal dominant	Huntington's disease (HD)	30–50 gradually progressive over 20 years	Cognitive psychiatric		Huntingtin	Genetic test
	Huntington disease like 2 (HDL2)	Early adulthood African origin	Cognitive Psychiatric	Sometimes Acanthocytes	Junctophilin-3	Genetic test
	Benign hereditary chorea	Childhood improvement in adult	Dystonia myoclonia tics learning difficulties	Thyroid, lung	NKX2-1	Genetic test
	Dentato-rubro-luysian atrophy	Early adulthood	Seizures dementia psychiatric		Atrophin-1	Genetic test
	SCA17	Childhood–early adulthood	Ataxia cognitive decline		SCA17	MRI, genetic test
	Paroxysmal kinesiogenic dyskinesia	Childhood	Short, frequent attacks upon movement		PRRT2	Genetic test
	Neuroferritinopathy	Adulthood	Akinesia MRI Increased T2		Ferritin light chain (FTL)	MRI Genetic test
Autosomal recessive	Chorea-acanthocytosis	Adulthood	Dystonia, orofacial predominance Self-mutation Neuropathy Myopathy	Acanthocytes	Chorein	Western blot Genetic test
	Ataxia telangiectasia	Childhood	Ataxia, neuropathy Oculomotor apraxia, myoclonus	Malignancies Immuno-globulin deficiencies	ATM	Genetic test
	Pantothenate kinase associated neurodegeneration	Childhood	Dystonia pyramidal tract Akinesia MR: eye of the tiger sign	Acanthocytes	PANK2	MRI Genetic test
	Wilson's disease	Childhood–young adult	Cognitive psychiatric	Liver haemolytic anemia	ATP7B	Ceruloplasmin level Copper extraction Gene test
X	McLeod syndrome		Dystonia, polyneuropathy, myopathy epilepsy	Acanthocytes	XK gene	Genetic test
Miscellaneous	Mitochondrial cytopathies	Variable, often in adulthood fluctuating	Tremor Neuropathy Myopathy	Frequent involvement of other systems	Mitochondrial genome Nuclear genes	Genetic test
	Inherited metabolic disorders	Most often childhood	Multiple	Frequent involvement of other systems	Numerous gene defects	Metabolic and genetic tests

support during the process, although this can also be offered by the counsellor themselves. They should be well knowledgeable on the multimodal aspects of the disorder and its course including its genetic background and research performed towards novel treatment strategies. Obviously, local regulatory aspects need to be recognized and respected. It is important to stress that the test is taken as an expression of the free will of the counselee and not under pressure by their environment. Further, the option to know or not to know remains open until definitive disclosure of the result. The counsellor should be at the disposal of the counselee in a simple and rapid fashion during the weeks of the counselling process and it is also important to ensure that a follow-up session is held after some time. The question of whether to test minors has been debated, but it is felt important not to impose a burden on children with information they may not wish to have at this moment of their life. One major risk of genetic testing of healthy potential carriers is the occurrence of suicide, and this is increased in people with a psychiatric history in the 5 years prior to the test and unemployed status [Almqvist *et al.* 1999, 2003].

Phenotypic assessment

Extending from the clinical examination run for the diagnostic process, there is a need to perform precise assessment and documentation of the phenotype at the time of diagnostic work-up and during the course of the disease. This is especially true in chronic progressive disorders presently without causal therapy like HD in order to offer problem-oriented symptomatic treatment. Furthermore, patients are often not aware of the severity of their symptoms and the possible dangers to which they are at risk [Hoth *et al.* 2007; Snowden *et al.* 1998]. The United Huntington's Disease Rating Scale (UHDRS) captures motor, functional, behaviour and cognitive symptoms [HSG, 1996]. The major advantage is that these instruments are complemented by precise instructions, which have been further implemented in assessment training programmes, available as a video with the original publication [HSG, 1996] and also online (see http://www.euro-hd.net) for EHDN registered members. They may be complemented by specific scales, such as the problem-oriented behavioural scale, a semistructural interview capturing symptoms [Hoth *et al.* 2007] related to altered affect, thought content and coping styles [Quinn *et al.* 1996]. Standardized use of these instructions leads to decreased assessment variability and ensures comparability over the course of the disorders in a particular subject.

Important aspects of the phenotype have been recognized and better described recently. They include the two age extremes of young and old, with profound phenotype differences, which need to be taken into account for management. Juvenile onset HD may be defined as the presence of disease manifestation at or before the age of 20, while childhood onset is defined as before the age of 10. The disease, at this age, tends to be more of a bradykinetic type with dystonia, with less prominent chorea, sometimes with myoclonus and epilepsy. They have behaviour and cognitive problems impairing school performance [Ribai *et al.* 2007]. There are even more extreme forms, for example a recently published report of an 18-month-old baby with severe developmental delay [Nicolas *et al.* 2011]. At the other end of the range, old people with a mutation in the HD gene may have a phenotype quite similar to senile chorea [Lefaucheur *et al.* 2012].

General management

All attempts should be made to remove the cause of chorea if possible. In most cases symptomatic treatment remains the sole option, as is specifically the case at present in HD and many of the hereditary choreas. Since the phenotype and the course of the disorder may be highly variable between different persons, sometimes even within a single family, it is important to target the symptomatic treatment according to the needs of the patient. Care has to be multidisciplinary, since a number of functions are affected either primarily as part of the direct effects of the mutation, or secondarily as complications occurring during the course of the disease. A problem-oriented treatment approach is mandated in all types of disorders with chorea, which cannot be controlled in a sufficient way by means of causal therapies. This includes a thorough examination of the phenotype, which should be repeated over the course of the disorder, best in using established instruments as described above. They should be used appropriately according to the age of the patient, the severity of his condition, and his comorbidity. Assessment of the psychosocial situation is also important, since care-givers play a major role in management.

For chronic disorders, participation in clinical trials or in cohorts to explore aspects of the phenotype may be motivating for the patient and their family. The Registry protocol, run by the European Huntington's Disease Network and the Cohort study by the Huntington Study group have provided such an option in the past. EnrolHD is a global observational study of the HD phenotype, which has now been launched. These comprehensive efforts, in which affected people and their families and carers participate, have a major training component, which helps in the development of centres with improved skills in the examination of HD patients, with clear consequences for improvement in management. Patients with HD should be followed up by such centres with a multidisciplinary team, the members of which are involved in different intensities along the course of the disease. Before onset and in the first stage of the disorder, they include neurologist, psychiatrist and geneticist, later physiotherapist, speech and occupational therapists, nursing and other medical specialists according to the multiple and increasing needs of gradually dependent patients. Palliative care and end of life stage management receives increasing attention [Marks *et al.* 2011].

Treatment can be classified as causal or symptomatic, but it is increasingly being recognized that there is overlap between these categories. Causal therapy aims at removing the cause of the disorder and, in the case of chorea, it is possible in few disorders, which are therefore important to recognize. The best-known example is L-dopa-induced dyskinesia in Parkinson's disease typically presenting as chorea. It can often be managed by adjustment in therapy [Prashanth *et al.* 2011]. Dopamine-antagonist-induced dyskinesia should prompt the removal of the offending drug, although, sometimes it can persist even after a very brief exposure to the drug. Some of the metabolic and toxic disorders listed in Table 2 may also be amenable to relatively simple treatment indicated for the underlying disorder. Wilson's disease should be treated by removing copper with penicillamine, trientene or zinc salts [Rosencrantz and Schilsky, 2011]. In chorea complicating autoimmune disease, the treatment has to be directed according to guidelines particular for each disorder. In genetic disorders, causal therapy would include gene therapy, specifically the removal or repair of the incriminated gene; at the present time, this is not possible, but studies are underway.

Table 2. Selection of more common sporadic disorders with prominent chorea.

	Disease
Drug induced	L-dopa induced chorea in Parkinson's disease
	Dopamine antagonists induced tardive dyskinesia
	Antiepileptic drugs
	Calcium channel blockers
	Psychostimulants
	Contraceptives
Autoimmune disorders	Sydenham chorea
	Systemic lupus erythematosus
	Antiphospholipid antibody syndrome
	Paraneoplastic
Infections	HIV
	Toxoplasmosis
	Syphilis
	Cystercosis
	Diphtheria
Metabolic disorders	Hyperthyroidism
	B12 deficiency
	Nonketotic hyperglycinemia
	Hypoglycinemia
	Hyponatremia
	Acute intermittent porphyria
	Hypocalcaemia
	Intoxications (carbon monoxide, heavy metals)
	Liver, kidney failure
Structural lesions	Cerebrovascular insult in basal ganglia
	Tumour

Two categories of approach can be seen among the symptomatic therapies. One is a specific approach, based on knowledge of the disease molecular mechanisms or on studies examining an aspect of the phenotype in a specific disease, the other is one that is based on the phenotypical characterization and generalization from other disorders, in which aspects of the phenotype are shared. Among the first is the treatment of paroxysmal chorea in patients with paroxysmal exercise-induced dyskinesia by prescribing carbamazepine, which is highly effective [Chen *et al.* 2011]. There are only very few clinical therapeutic trials, which have assessed treatment symptomatic treatment in HD [Nance, 2012], therefore we must rely on expert opinion sometimes more or less appropriately

based on studies on chorea or psychiatric symptoms in patients suffering from other disorders. It is important, therefore, to keep this in mind, since treatment of one aspect of the symptom would most probably affect the expression of another, which could not have been assessed in these trials. Overall, the evidence available to provide suggestions for the symptomatic treatment on HD is poor [Mestre *et al.* 2009b]. The major aim remains to improve quality of life, which can be assessed by some newly developed instruments, specifically in HD.

The treatment of motor symptoms

Faced with the paucity of good evidence to prepare guidelines to treat movement disorder in HD [Bonelli and Hofmann, 2007; Bonelli and Wenning, 2006; Venuto *et al.* 2012], we have performed a survey on the use of drugs to treat chorea in different continents [Burgunder *et al.* 2011]. Survey results showed that patient's need, including stigma, physical injury, gait instability, work interference and disturbed sleep were indications to start antichoreic drugs, but there were profound differences in their choice. There was an agreement on the importance of assessing additional aspects of the phenotype to guide the choice. For example, an antipsychotic drug was preferred when comorbid psychotic or aggressive behaviours were present. Tetrabenazine is the only drug approved by the US Food and Drug Administration for the treatment of chorea in HD [Poon *et al.* 2010]. The major mechanism of action of tetrabenazine is the inhibition of a vesicular monoamine transporter (VMAT). Brain VMAT2 is active in cytoplasmatic dopamine transport and storage in synaptic vesicles. In a short-term randomized control trial involving 84 patients over 12 weeks, tetrabenazine, at adjusted doses up to100 mg per day, was shown to decrease the UHDRS chorea subscore by 5 points (placebo 1.5) [HSG, 2006]. There was also an improvement in the global clinical impression. After discontinuation of the drug, chorea worsened again. In a second, smaller randomized, controlled trial of tetrabenazine withdrawal, a worsening of 5 points was found [Frank *et al.* 2008]. Tetrabenazine has also been suggested to treat chorea in benign hereditary chorea [Gras *et al.* 2012]. The major side effects of the drug include bradykinesia with tremor and depression. The first needs a careful balancing between the different aspects of the abnormal movements with dose titration done accordingly. Mild depression before or after the start of tetrabenazine therapy should not preclude prescription of the drug, but a combination with an antidepressant should be used in case tetrabenazine shows a good effect on chorea. A recent review of the guideline development subcommittee of the American Academy of Neurology on the pharmacologic treatment of chorea in HD [Armstrong and Miyasaki, 2012] suggests, together with tetrabenazine, a number of other drugs, including amantadine, riluzole and nabilone, but tends to dismiss neuroleptic drugs. In our survey, with regard to the available evidence and the day-to-day experience, only few experts favoured the use of amantadine, most had no experience with it, probably because they did not use it in due to a lack of evidence in the first place [Burgunder *et al.* 2011]. Likewise, the majority of participating experts did not favour riluzole. Indeed, in a randomized, controlled study only a weak effect for reduction of chorea was found [Landwehrmeyer *et al.* 2007]. The effect of nabilone was only very weak, decreasing chorea subscores by only 1.68 points [Curtis *et al.* 2009].

On the other hand, a large experience in the use of neuroleptic drugs motivated the experts to use it with their perception as being efficacious [Bonelli and Hofmann, 2007; Bonelli and Wenning, 2006]. Tetrabenazine can be considered as the first choice drug in chorea, in the absence of severe depression, psychosis or aggressive behaviour. In the latter instances, an antipsychotic drug may be preferred, for example olanzapine (2.5–10 mg), risperidone (0.5–2 mg) or tiapridal (50–200 mg). Doses need to be adapted to the response and, sometimes, it may be useful to try several antipsychotic drugs to find the most appropriate one in a selected patient. Doses need to be optimized during the course of the disorder and side effects have to be considered. Combination therapies, including adjunction of benzodiazepines, may be needed in specific situations. In the presence of disabling myoclonus, valproate may be used [Saft *et al.* 2006].

It must be borne in mind that chorea typically decreases in the course of the disorders, making adjustment in therapy mandatory. In advanced cases, akinesia, with severe rigidity and spasticity, will not respond to tetrabenazine, which has to be tapered off. This is true also for neuroleptic drugs, except when given against other symptoms. No controlled trial has been performed to provide evidence to guide treatment decisions of movement disorders in these late disease stages. Experience shows that some patients will respond to baclofen or

benzodiazepines, and it is worthwhile to prescribe the drugs and closely observe the effects and side effects, usually related to sedation, falls not being a major issue at this stage, since most of the persons affected have lost gait ability at this advanced stage. Chemodenervation using botulinum toxin injection in hyperactive muscles may sometimes be useful for focal spasms, including bruxism or focally predominant spastic overactivity.

Lack or appropriate, well-validated assessment methods of the effect of physiotherapy has hampered the conduction of high-quality trials and also the evaluation of its place in the practical clinical management of patients with HD and other disorders with chorea. However, in a recent study, a battery of clinical assessment complemented with simple technical measurements has been used in a small trial, leading to the suggestion that a predefined intervention with a focus on posture and gait was beneficial for patients with HD [Bohlen *et al.* 2012]. While this study is still preliminary, it should be seminal for the future development in this field of nonpharmacological interventions aiming at improving function in patients with chorea. Present evidence and expertise has been explored by one of the EHDN working parties recently [Quinn and Busse, 2012a]. The group has offered provisional guidelines with suggestions for patients in each stage of the disorder and stressing the need to tailor therapy to the individual patient [Quinn and Busse, 2012b]. Motor problems are classified under seven items, including: exercise capacity and performance; planning and sequencing of tasks; mobility, balance and falls risk; secondary adaptive changes and deconditioning; impaired postural control and alignment in sitting; respiratory dysfunction; and end-stage care. For each of the items, aims are defined and appropriate strategies described. While these guidelines represent a major advance for the rational use of physiotherapy in HD, they have all of their value for the other chronic choreatic disorders, in which evidence is even less established.

Deep brain stimulation targeting the globus pallidus has a long-term effect on dyskinesia in Parkinson's disease [Volkmann *et al.* 2004], which may be retained even in cases with progressing cognitive decline [Loher *et al.* 2002]. Subthalamic nucleus stimulation, which is now more often used in Parkinson's disease [Bronstein *et al.* 2011], allows the doses of L-dopa and other dopaminergic drugs to be decreased, with the consecutive indirect improvement of drug-induced dyskinesia. Stimulation of the globus pallidus is an established treatment in generalized and in some forms of focal dystonia [Krauss *et al.* 1999], and early reports suggested a modest benefit in choreoathetosis [Krauss *et al.* 2003] and in chorea acanthocytosis [Li *et al.* 2012]. Side effects include dysarthria, gait disorders, hypotonia and cognitive impairment, all of which seem to be more frequent and of earlier occurrence when compared with Parkinson's disease. So far only uncontrolled studies of small cohorts have been published and assessment has been done mostly without blinding to the treatment applied. There may also be a publication bias and more studies are needed, addressing questions including the choice of patients (in HD probably the group with more prominent chorea having less pronounced cognitive deficits [t'Hart *et al.* 2012]), and stimulation parameters (high *versus* low frequency) [Edwards *et al.* 2012].

Cognitive disorders

There are only few studies on the pharmacological treatment of cognitive impairment in HD, and none has shown any benefit [Nance, 2012]. In a recent study, treatment with latrepirdine for 6 months did not improve cognition or function relative to placebo [HORIZON Investigators of the Huntington Disease Study Group and European Huntington's Disease Network, 2012]. Assessment is important, in order to counsel the patients and family about occupation adaptation if still working and also about the development of coping strategies. Cognitive therapy may be useful in order to help the patient and his environment to structure activities and manage available resources. Environmental strategies may also be of value in advanced cases.

Treatment of psychiatric and behaviour symptoms

Evidence on which to base the treatment of psychiatric symptoms in HD and other chorea is very poor, and most guidelines rely on personal expertise and on suggestions extrapolated from studies in disorders with a mostly psychiatric phenotype. A similar survey such as that regarding the therapeutic approach of chorea mentioned above [Burgunder *et al.* 2011] was done by investigators from the HSG and EHDN on obsessive compulsive behaviours [Anderson *et al.* 2011] and a similar variety of therapies used across different countries. Based on that survey, a step-wise procedure was

suggested, with a serotonin reuptake inhibitor as the first choice, combined with behavioural therapy, at least in patients with only mild cognitive impairment. The response to a low dose is assessed and adjustments made as appropriate. In the case of insufficient response, the experts felt it would be appropriate to switch to another drug of the same category or to another antidepressant. In nonresponsive cases, or when other symptoms need treatment combination with another substance is suggested. A similar approach was taken for irritability [Groves *et al.* 2011] and antipsychotic medication in the case of comorbid severe aggressive behaviours, psychosis or impulsivity. In the presence of additional depression, anxiety or obsessive compulsive behaviours, a serotonin reuptake inhibitor is suggested as first line. For both groups behavioural management strategies are advisable [Groves *et al.* 2011]; this may include protection from stress factors in advanced cases in the need of institutionalized chronic care. After dose optimization the next step would be combination therapy. Similar approaches may be used for the treatment of depression.

Other problems

Dysphagia occurs in a later stage of the disease and may be due to involuntary orofacial movement disorder, decrease in motor control, propensity to eat rapidly and the side effects of drugs, including xerostoma due to anticholinergic effects. There is no controlled study to guide choices in dysphagia, but established methods include providing swallowing tips (which should be started before cognitive impairment precludes learning), to prepare food in appropriate ways and to eat in a quiet and supervised environment. Gastric feeding needs to be discussed early, in order to understand patient's choices and the danger of choking and aspiration pneumonia as potential causes of complications. Weight loss is frequent in HD and is due to dysphagia, choreatic movement but also to a modulation of metabolism. It is important to appropriately increase energy intake in a way suitable for the patient. There are a number of sociomedical problems faced by the patients and their relatives, which need to be addressed in appropriate ways by trained professionals.

Novel therapeutic strategies

At the present time, there is insufficient evidence to adopt any disease-modifying treatment in HD [Mestre *et al.* 2009a]. However, HD is a monogenetic degenerative disorder, which can be diagnosed well in advance of any symptom, and so this disorder may therefore be considered as a paradigm for novel neuroprotective treatment. At this time, no such treatment is available, although, the dramatic increase in our understanding of the molecular pathways involved in the pathogenesis of this disorder, and the availability of several animal models to perform preclinical testing of emerging therapeutic strategies, may nurture some hope for the future. Furthermore, our improved understanding of the phenotype and the course of the disorder, including the development of biomarkers allow the preparation of improved strategies in implementing therapeutic trials. The choice of biomarkers for protective studies will have to be tailored to which aspect of the neurodegenerative disease process and of the consecutive neuroplastic adaptation needs to be approached. An intensive, 3-year study of a cohort of HD gene carriers in a premanifest and in an early stage of the disease has recently been published [Tabrizi *et al.* 2009, 2011, 2012]. These data allow the suggestion that MRI assessments, including whole-brain atrophy, ventricular expansion, caudate atrophy, putamen atrophy, and white-matter atrophy, are valuable biomarkers both in the presymptomatic and in the early manifest stages. In the first, a cognitive test may be added, for example the symbol digit modality test, the Stroop word reading and emotion recognition [Tabrizi *et al.* 2012]. A follow-up protocol to these important studies is now in place and additional data are expected in the near future. They will inform the protocol of future clinical trials aimed at disease modification. The approach to disease-modifying treatment is anyway going to be multifaceted. Promising developments include gene silencing, decrease of expressed mutated protein, and the provision of trophic factors [Appl *et al.* 2012]. Several strategies have been followed in using transplantations of stem cells for the replacement of the degenerated neurons. Alternatively, transplantation of cells as a mean of trophic factors provision, for example astrocytes producing BDNF, has also been explored in animal studies [Giralt *et al.* 2010]. However, despite promising results from preclinical studies in animals, long-term studies in people with HD have been rather disappointing. Bilateral transplantation of embryonic tissue in the caudate of HD patients lead to a short benefit in some, but not all patients in a pilot study [Bachoud-Levi *et al.* 2006]. One reason is the fact, that neuronal transplants undergo a disease-related degeneration similar to the host [Cicchetti

et al. 2009]. Novel technologies allow the preparation of mesenchymal stromal cells to treat a number of disorders and phase I–III studies are underway, for example to treat chronic liver disease [Takami *et al.* 2012] or multiple sclerosis [Connick *et al.* 2011].

While these options are not yet available for clinical application, a prudent optimism to be able to develop disease-modifying treatments of HD may now be warranted on some rational basis. In the meantime a strong commitment of dedicated teams to take care of these patients, develop comprehensive care management at all levels of the course of the disorders, and inclusion in prospective observational protocols such as Registry and EnrollHD, provides hope for affected people and their families.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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