Current Topics in Behavioral Neurosciences 22

Hoa Huu Phuc Nguyen
M. Angela Cenci *Editors*

Behavioral Neurobiology of Huntington's Disease and Parkinson's Disease

Springer

Current Topics in Behavioral Neurosciences

Volume 22

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Behavioral Neurobiology of Huntington's Disease and Parkinson's Disease

Springer

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ISSN 1866-3370 ISSN 1866-3389 (electronic)
Current Topics in Behavioral Neurosciences
ISBN 978-3-662-46343-7 ISBN 978-3-662-46344-4 (eBook)
DOI 10.1007/978-3-662-46344-4

Library of Congress Control Number: 2015939990

Springer Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer-Verlag GmbH Berlin Heidelberg is part of Springer Science+Business Media (www.springer.com)

Preface by the Editors

Parkinson's disease (PD) and Huntington's disease (HD) are the paradigms of opposite movement disorders originating in the basal ganglia. On one hand, poverty and slowness of movement (hypokinesia and bradykinesia) are pathognomic to PD and related conditions. On the other hand, excessive and uncontrolled movements are a hallmark of HD. Indeed, the latter condition is the most common genetic cause of involuntary, fleeting and writhing movements (chorea), which is why the disease used to be called 'Huntington's chorea'. Both PD and HD are not only disorders of movement, however. In both conditions, mental processing and mood are affected, and metabolic or autonomic dysfunction cause a range of non-neurological symptoms.

From both etiological and epidemiological standpoints, PD and HD appear as two widely different conditions. PD is the second most common neurodegenerative disease after Alzheimer's and currently affects about 6.3 million people worldwide. It is an age-related disorder lacking an identifiable cause ('idiopathic') in 90 % of the cases. By contrast, HD is a relatively rare familial disease caused by an autosomal dominant mutation in the *HTT* gene. Symptoms of HD commonly become manifest between the ages of 35 and 50 years, but they can begin at virtually any age depending on the CAG repeat length (see below).

The genetic basis of HD was discovered in 1993 by an international collaborative effort spearheaded by the Hereditary Disease Foundation. Since then, several other neurological diseases were found to depend on a similar genetic defect, consisting in the expansion of a CAG (cytosine-adenine-guanine) triplet repeat stretch within the disease-causing gene.

During the past 17 years, it has become increasingly clear that PD has a strong genetic component, too. Since 1997, several genetic mutations have been positively associated with PD in affected families. Beside these monogenic cases, genetic susceptibility has been suggested to underlie the common idiopathic forms of PD. Indeed, recent genome-wide association studies have established that certain common gene variants occur with an increased frequency in people with idiopathic PD. It is however clear that environmental factors, such as exposure to certain toxins, may underlie many cases of idiopathic PD.

Despite their different etiologies, PD and HD have many things in common. Both diseases heavily affect the network functions of the cortico-basal ganglia-thalamo-cortical circuitry. Disturbances in corticostriatal synaptic transmission and atrophic changes of striatal projection neurons are key players in their pathophysiology. And although different events may trigger the primary neurodegenerative process, there are striking commonalities in the pathogenic pathways involved. The commonalities include, misfolding and aggregation of proteins, deficient protein degradation, neuroinflammation, mitochondrial dysfunction, glial pathology, deficits in axonal transport, loss of synapses, glutamate dyshomeostasis, and altered signaling downstream of both dopamine and glutamate receptors. It is therefore not surprising that PD and HD continue to attract the attention of overlapping communities of basic and clinical investigators. In both disease areas, current basic research aims at either determining the mechanisms of neurodegeneration, or improving animal models that will expedite the mechanistic studies. This basic research has already spurred a number of clinical trials of either symptomatic treatments, or approaches to slow the progression of the disease. However, none of the putative disease-modifying approaches thus far tested have yet translated into successful treatments for the human diseases. It is therefore very important to intensify research efforts that can lead to an improved understanding of the pathobiology of PD and HD, revealing new potential therapeutic targets. This kind of research is heavily dependent on the possibility to reproduce key features of PD and HD in simpler models that are accessible to in-depth biological investigation. Animal models are indispensable to unravel non-cell autonomous mechanisms of disease, and the relationship between neurodegeneration and behavioural impairment, or overt neurological deficits can only be addressed in whole-animal models of disease.

We hope that this volume will aid the research on HD and PD by providing an up-to-date coverage of current animal models that can be used to investigate particular pathways, and to link them to both system-level pathophysiology and behavioural abnormalities. No animal models will ever reproduce all the complexity of a human neurological disease, and it is therefore very important for the research community to rely on an articulate repertoire of models tailored to mimic the specific features to be investigated in each study.

The HD part opens with a comprehensive overview of the clinical features of HD by Ghosh and Tabrizi (“Clinical Aspects of Huntington’s Disease”) including available symptomatic treatments and new data from large clinical natural history studies, which have identified potential biomarkers and predictors of disease onset and progression to guide future therapeutic interventions. The next chapter (“The Neuropathology of Huntington’s Disease”, by Waldvogel, Kim, Tippett, Vonsattel, Faull) then provides a detailed description of the current knowledge of neuropathological changes in human HD brains and emphasizes the association of the heterogeneous nature of HD symptomatology with the heterogeneous nature of the neurodegeneration that occurs throughout the different regions of the brain in different HD patients. Chapter by De Souza and Leavitt (“Neurobiology of Huntington’s Disease”) then outlines our current knowledge on the normal

function of huntingtin and the main pathomechanisms by which mutant huntingtin may mediate neurodegeneration in HD.

With the basis set in the three previous chapters, Brooks and Dunnett review in their chapter ("Mouse Models of Huntington's Disease") the similarities and differences in the neurobiology found in the mouse models of HD and the human disease state. Their review also discusses how abnormalities in functional circuitry and neurotransmitter systems impact on the behavioural readouts across the mouse lines and how these may correspond to the deficits observed in patients. While mouse models have provided invaluable information on the pathogenesis and pathophysiology of HD, they might not be the most adequate species for mimicking the human disease. Rats for example have more developed motor learning and motor capabilities. Assays of cognition are more robust in rats than mice, and test more advanced functional aspects. Carreira, Jahanshahi, Zeef, Kocabicak, Vlamings, von Hörsten and Temel provide a comprehensive review ("Transgenic Rat Models of Huntington's Disease") on the transgenic rat models for HD that have been generated so far. However, both rat and mouse model of HD lack the striking neuronal cell loss observed in HD patients. Chapter "Large Animal Models of Huntington's Disease" by Li and Li reviews important findings from these pig, sheep and non-human primate models including a discussion on why neurodegeneration is more readily observed in these models than in rodent models for HD.

Last but not least, Mrzljak and Munoz-Sanjuan provide a thorough and comprehensive review of the current state of therapeutic development for the treatment of HD including ongoing randomized clinical trials in HD as well as the past and present preclinical development of small molecules and molecular therapies at CHDI with an outlook on future directions.

The PD part opens with Chap. "Clinical and Pathological Features of Parkinson's Disease", by Schneider and Obeso, which sets the stage for all the following ones. This chapter reviews the pathological and symptomatic features that need to be considered when creating or validating experimental models of PD. In the next chapter, Johnson and Fox review state-of-the-art symptomatic models of PD having utmost face validity to the human condition ("Symptomatic Models of Parkinson's Disease and L-DOPA-Induced Dyskinesia in Non-human Primates").

Chapter by Cebrian, Loike and Sulzer ("Neuroinflammation in Parkinson's Disease Animal Models: A Cell Stress Response or a Step in Neurodegeneration?") compares and summarizes findings on neuroinflammatory responses in a wide range of toxin-based and genetic models of PD. The following Chap. "Viral Vector-Based Models of Parkinson's Disease" (by Van der Perren, Van den Haute, Baekelandt) provides an overview of current viral vector-based PD models in rodents, both those based on overexpression strategies for autosomal dominant genes (such as α-synuclein and LRRK2) and those based on knockout or knockdown strategies for autosomal recessive genes, such as parkin, DJ-1and PINK1.

The severe cognitive decline occurring in advanced stages of PD is associated with cortical and limbic alpha-synuclein pathology. Hatami and Chesselet have therefore chosen to summarize the cognitive deficits observed in several transgenic mouse lines overexpressing wild-type or mutated alpha-synuclein. The authors also

discuss how these models relate to the disease process in humans ("Transgenic Rodent Models to Study Alpha-Synuclein Pathogenesis, with a Focus on Cognitive Deficits").

In addition to alpha-synuclein, the gene coding for leucine-rich repeat kinase 2 (LRRK-2) is implicated in autosomal dominant forms of PD. A comprehensive summary of the different models employed to understand *LRRK2*-associated PD is provided by Daniel and Moore ("Modeling LRRK2 Pathobiology in Parkinson's Disease: From Yeast to Rodents"). This chapter covers a wide variety of experimental models, including yeast, invertebrates, transgenic and viral-based rodents, and patient-derived induced pluripotent stem cells.

The PD section of the volume closes with Chap. "Models of Multiple System Atrophy" (by Fellner, Wenning, and Stefanova). This chapter gives an overview of the atypical Parkinson's syndrome, Multiple System Atrophy (MSA) and summarizes the currently available MSA animal models and their relevance for preclinical testing of disease-modifying therapies.

As with any book, it is impossible to cover every aspect of the current literature, and some important lines of research may not have been sufficiently covered here due to space restrictions. We are very grateful to all our dedicated colleagues who have made great contributions to this book. We think that all chapters provide an accurate and thorough overview of our current knowledge of the behavioural neurobiology of Huntington's and Parkinson's Disease and hope that the readers will enjoy each chapter as we did, and that this book will be helpful to them in their research efforts to understand and find treatments for these devastating diseases.

Hoa Huu Phuc Nguyen
M. Angela Cenci

Contents

Part I Behavioral Neurobiology of Huntington's Disease

Clinical Aspects of Huntington's Disease 3
Rhia Ghosh and Sarah J. Tabrizi

The Neuropathology of Huntington's Disease 33
Henry J. Waldvogel, Eric H. Kim, Lynette J. Tippett, Jean-Paul G. Vonsattel and Richard LM Faull

Neurobiology of Huntington's Disease 81
Rebecca A.G. De Souza and Blair R. Leavitt

Mouse Models of Huntington's Disease 101
Simon P. Brooks and Stephen B. Dunnett

Transgenic Rat Models of Huntington's Disease 135
João Casaca Carreira, Ali Jahanshahi, Dagmar Zeef, Ersoy Kocabicak, Rinske Vlamings, Stephan von Hörsten and Yasin Temel

Large Animal Models of Huntington's Disease 149
Xiao-Jiang Li and Shihua Li

Therapeutic Strategies for Huntington's Disease 161
Ladislav Mrzljak and Ignacio Munoz-Sanjuan

Part II Behavioral Neurobiology of Parkinson's Disease

Clinical and Pathological Features of Parkinson's Disease 205
Susanne A. Schneider and Jose A. Obeso

Symptomatic Models of Parkinson's Disease and L-DOPA-Induced Dyskinesia in Non-human Primates 221
Tom M. Johnston and Susan H. Fox

Neuroinflammation in Parkinson's Disease Animal Models: A Cell Stress Response or a Step in Neurodegeneration? 237
Carolina Cebrián, John D. Loike and David Sulzer

Viral Vector-Based Models of Parkinson's Disease 271
Anke Van der Perren, Chris Van den Haute and Veerle Baekelandt

Transgenic Rodent Models to Study Alpha-Synuclein Pathogenesis, with a Focus on Cognitive Deficits 303
Asa Hatami and Marie-Francoise Chesselet

Modeling LRRK2 Pathobiology in Parkinson's Disease: From Yeast to Rodents 331
Guillaume Daniel and Darren J. Moore

Models of Multiple System Atrophy 369
Lisa Fellner, Gregor K. Wenning and Nadia Stefanova

Index 395

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Part I
Behavioral Neurobiology of Huntington's Disease

Clinical Aspects of Huntington's Disease

Rhia Ghosh and Sarah J. Tabrizi

Abstract Huntington's disease (HD) is a devastating inherited neurodegenerative condition characterized by progressive motor, cognitive, and psychiatric symptoms. Symptoms progress over 15–20 years, and there are currently no disease-modifying therapies. The causative genetic mutation is an expanded CAG repeat in the *HTT* gene encoding the Huntingtin protein, and is inherited in an autosomal dominant manner. In this chapter we discuss the genetics, clinical presentation, and management of this condition, as well as new data from large-scale clinical research studies on the natural history of HD.

Keywords Huntington's disease · Chorea · Genetics · Symptoms · Management · Natural history

Contents

1 Introduction 4
2 Epidemiology 4
3 The Genetic Origins of Huntington's Disease 5
4 Clinical Presentation 6
4.1 Motor Features 6
4.2 Cognitive Features 9
4.3 Psychiatric Features 9
4.4 Other Neurological Symptoms 10
4.5 The Peripheral Phenotype of Huntington's Disease 11
4.6 Juvenile Huntington's Disease 11
5 Disease Progression 12
6 Diagnosis and Investigations 13
7 Management 14

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Curr Topics Behav Neurosci (2015) 22: 3–31
DOI 10.1007/7854_2013_238
Published Online: 24 August 2013

7.1 Drug Treatments 15
7.2 Non-Drug Treatments 17
7.3 End of Life Care 21
7.4 Genetic Testing 22
8 New Data on Mapping Huntington's Disease from Clinical Natural History Studies 24
8.1 Biomarkers, and Predictors of Disease Onset and Progression 24
9 Conclusion 28
References 29

1 Introduction

Huntington's disease (HD) is a devastating inherited neurodegenerative condition characterized by progressive motor, cognitive, and psychiatric symptoms. It was formally described for the first time in 1872 by George Huntington, at the time a newly qualified doctor in the USA (Huntington 1872). The clinical features that he observed remain true today and sadly the disease is still "*one of the incurables*", although several studies to find disease-modifying treatments are underway.

Since the original description, the name of this condition has been changed from Huntington's chorea to Huntington's disease to acknowledge the multiple non-motor symptoms faced by patients with this disease; these may cause as much if not greater distress to patients and their families, and management must be tailored to meet these needs appropriately (Novak and Tabrizi 2010). In this chapter we detail the genetic origins, clinical presentation, and current management of HD.

2 Epidemiology

The prevalence of HD is variable across the world. Japan, South Africa, and Finland have naturally very low rates of disease. It has previously been thought to affect 4–10 per 100,000 people in the Western hemisphere (Harper 2002); however, recent data from the UK suggest a higher prevalence at 12.3 per 100,000 (Evans et al. 2013; Rawlins 2010). For many reasons, including those dating back to the seventeenth century when witchcraft was thought to be associated with HD, there has been an enormous amount of stigma attached to this condition (Wexler 2010). This has led to patients and families with HD attempting to conceal their situation rather than seek medical help, thus leading to lower estimations of prevalence.

It is thought that HD spread across the globe due to migration from North-West Europe. There are communities in which the prevalence of HD is exceptionally high; one of the most well-known is the population living near the edge of Lake Maracaibo in Venezuela where the prevalence is 700 per 100,000. It was in this group of people that genetic linkage studies ultimately led to the discovery of the

causative gene mutation for HD in 1993 (Gusella et al. 1983; The Huntington's Disease Collaborative Research Group 1993).

3 The Genetic Origins of Huntington's Disease

Huntington's disease is caused by an elongated CAG triplet repeat in exon 1 of the gene encoding Huntingtin protein ("*HTT*" is used to refer to the gene that encodes the protein "HTT"), which lies on the short arm of chromosome 4. The wild-type gene carries fewer than 36 repeats. Patient's with greater than 40 CAG repeats will develop HD at some point in their lives as the mutation is fully penetrant at these repeat lengths. Those patients who have 36–39 CAG repeats display a reduced penetrance—some may develop features of HD at an older age, others may never become symptomatic at all (Snell et al. 1993; Rubinsztein et al. 1996).

HD is inherited in an autosomal dominant fashion—that is to say, if one parent is affected, there is a 50 % chance that each of their children will be affected. Individuals with "intermediate allele" CAG repeat lengths of 27–35 were previously thought to be asymptomatic, though a recent study suggests that there may be a behavioral phenotype in this group of patients (Killoran et al. 2013). Due to the potential expansion of the CAG repeat length with cell division in meiosis, the offspring of patients who have an intermediate allele may inherit greater than 35 repeats causing symptoms to arise sporadically in a family with no apparent history of HD. Other seemingly sporadic cases of HD occur in cases of non-paternity. Sporadic cases can also arise when the affected parent, who passed on the mutation, died from other causes before developing symptoms, or were misdiagnosed as having primary psychiatric illness or dementia (among others). Therefore, it is important to ascertain a full and accurate family history during assessment. Approximately 6–8 % cases of newly diagnosed HD are sporadic cases (Almqvist et al. 2001; Siesling et al. 2000).

The instability of the CAG repeat length during meiosis can lead to longer repeat lengths in successive generations within a family; longer repeat lengths correlate with earlier age of onset of disease. This is a genetic phenomenon known as "anticipation". It is more likely to occur when the mutation is inherited down the paternal line—hypothesized to be due to differences between spermatogenesis and oogenesis (Kremer et al. 1995; Zühlke et al. 1993). 90 % of patients who have Juvenile HD (with an age of onset of <20 years old) have inherited this from their father (Barbeau 1970).

At a population level, roughly 50–70 % of the variability in age of onset has been shown to correlate inversely with the CAG repeat length; other factors accounting for the remaining variability are a subject of ongoing research and likely to be made up of both further genetic and environmental disease modifiers (Wexler et al. 2004). Therefore, it is not possible to predict age of onset of individual patients seen in clinic—an important point to stress if patients wish to know their CAG repeat length. This is especially true for patients whose repeat lengths range from 40 to 50 (the majority), as great variability is seen in this range.

More recently, the "conditional onset probability model" has been developed, which is more accurately able to estimate the percentage chance of disease-free survival over a set number of years (conventionally 5 years). The model is based on data from a large cohort of 3000 patients and takes into account not only the CAG repeat length, but the number of years disease free that a patient has already lived (Langbehn et al. 2004, 2010). However, even this more sophisticated model cannot accurately predict the age of onset for individual patients, and appropriate counseling must be given with regards to the limitations of this information if disclosing CAG repeat lengths to patients. Indeed, many patients may well be experiencing symptoms of HD before their official "onset" of disease—this is explored more fully below.

4 Clinical Presentation

Huntington's disease is characterized by a triad of progressive motor, cognitive and psychiatric symptoms, with slow but relentless deterioration over a period of 15–20 years. Ultimately, the cause of death is most commonly secondary to pneumonia (Lanska et al. 1988). The mean age of symptom onset is at 40 years, but HD has been diagnosed in children as young as 2 years old, and in adults up to the age of 87. If symptom onset occurs at <20 years of age, the condition is referred to as "Juvenile HD" (Kremer 2002).

Making a formal diagnosis of HD currently requires the presence of definitive extrapyramidal motor symptoms (Huntington Study Group 1996), but the reality is that psychiatric and cognitive symptoms often precede this. Subtle motor features that go undetected by the patient or their family may also be present for years before a diagnosis of "manifest" HD is made (Ross and Tabrizi 2011), as shown in Fig. 1. This is known as the "prodromal" phase of HD, and corresponds to neurobiological changes such as loss of corticostriatal connectivity and striatal atrophy (Tabrizi et al. 2012) (see Fig. 2).

Prior to this patients who are known to carry the genetic mutation are said to have "premanifest" disease, during which they have no subjective symptoms or objective signs on examination. More recently, the term "perimanifest" disease has been used by some, to describe the group of patients with prodromal HD who are felt by their clinician to be developing the extrapyramidal signs that will lead to a diagnosis of manifest HD in the near future (Tabrizi et al. 2012).

4.1 Motor Features

Motor features in HD comprise added involuntary movements and also impaired voluntary movements.

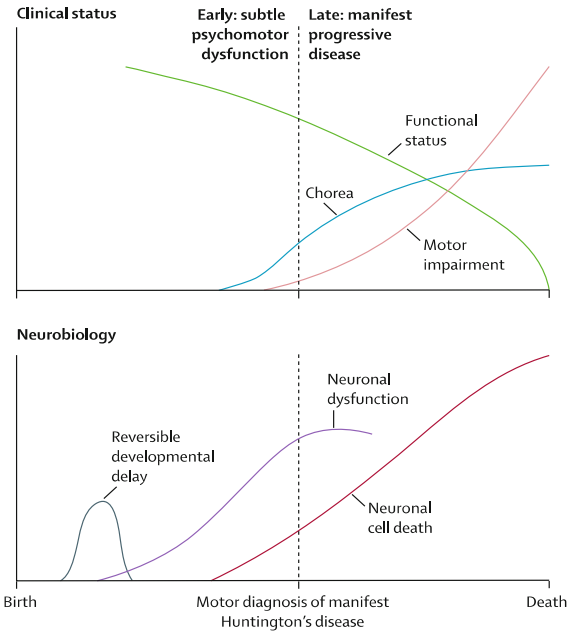

Fig. 1 Progression of Huntington's disease over a patient's lifespan, with corresponding neurobiological changes. Reprinted from Ross and Tabrizi (Ross and Tabrizi 2011) with permission from Elsevier

Initial features include involuntary added movements of the distal extremities and face, which may look like small twitches. Patients may try to incorporate these into their natural voluntary movements. They then spread more proximally, and become larger in amplitude, and the patient suffers from these choreiform movements all the time that they are awake. Chorea is defined as involuntary, excessive movements which are short-lived and can appear to be semi-purposeful. The pattern of the movements also varies, for example, facial muscle involvement can cause eye closure, head turning, and tongue protrusion, whereas involvement of axial muscles causes extension and arching of the back. The degree to which these movements bother the patients themselves is variable, especially in the early stages. However as chorea progresses it can cause problems with writing and eating, and frequently contributes to falling.

Dystonia is also observed—these are slower movements caused by increased muscle tone and sustained muscle contractions which lead to abnormal postures such as tilting or turning of the neck (torticollis) or arching of the back (opisthotonos). As the disease progresses, hyperkinetic movements lessen and instead bradykinesia (slowness of movement), akinesia (delay in initiating movement), and rigidity become more prominent. These later features tend to cause more problems than the more readily recognizable chorea (Novak and Tabrizi 2010).

"Myoclonus" or sudden brief jerking of groups of muscles is sometimes seen in HD, especially in the juvenile form. Likewise, "tics" which are defined as brief, intermittent, stereotyped movements such as blinking, head jerking, nose twitching, or even sniffs, snorts and grunts can develop. These involuntary tics are often

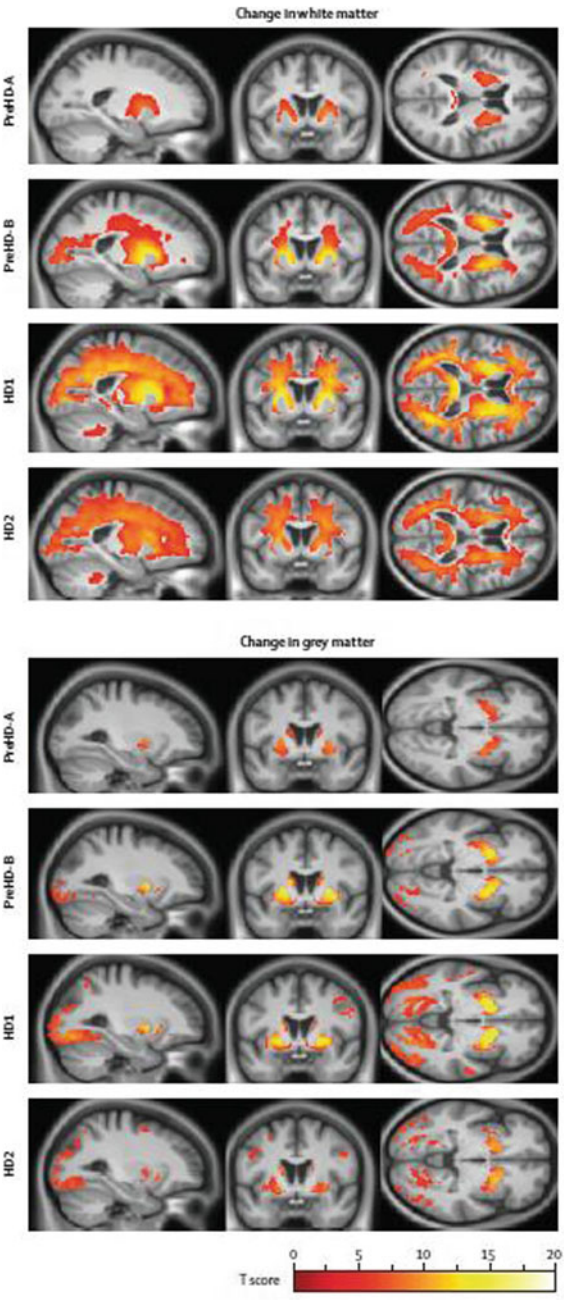

Fig. 2 Parametric maps showing regions with statistically significant atrophy in *grey* and *white* matter at baseline, 12 and 24 months (from *left* to *right* in each frame). PreHD-A and preHD-B are premanifest Huntington's disease gene carriers with estimated time to clinical disease onset greater than and less than 10.8 years, respectively. HD1 and HD2 are patients with early manifest disease who have no functional impairment and mild functional impairment, respectively. The striatum is affected early on, with more widespread atrophy at later stages. Reprinted from Lancet Neurology, Tabrizi et al. 2012 with permission from Elsevier

unnoticed by the patients themselves, but picked up by their carers who can find them irritating.

Gait is affected and may appear ataxic, leading to falls. Loss of postural reflexes also contributes to this. Patients may ultimately require a wheelchair to mobilize safely, and require help with their activities of daily living (ADLs).

Stress, anxiety, and intercurrent infections all lead to temporary deterioration of many of the symptoms mentioned above—a feature that is common to many movement disorders.

4.2 Cognitive Features

Cognitive symptoms may begin during the prodromal phase of HD (Paulsen et al. 2008; Harrington et al. 2012). They are variable in severity, and range from subtle deficits that may go unrecognized by the patient, to prominent impairment. Cognitive problems have been shown to adversely affect daily functional ability independently of motor impairment (Rothlind et al. 1993). Patients however often lack insight into this (and into their disease progression more generally) and for this reason it is important to take a collateral history from relatives and carers. This lack of insight also compounds the cognitive deficits.

The main changes are deficits relating to executive functioning, i.e. high-level cognitive processing which controls other aspects of cognitive functioning. This leads to problems with planning and initiating actions, impaired organizational skills, and inability to adjust to social changes due to the development of concrete thinking. Problems with multitasking are a common early feature in HD and can lead to significant problems in the workplace (Novak and Tabrizi 2010).

Other cognitive problems include general slowing of thought processes, impairments of short-term memory (leading to difficulties in acquiring new skills), and occasionally a decline in visuospatial skills. In particular, patients' perception of their own body in relation to their surrounding environment can be impaired, causing them to bump into objects, trip and fall. Semantic knowledge and language skills are relatively preserved (Craufurd and Snowden 2002).

As cognitive dysfunction progresses, patients can develop a severe frontal and subcortical dementia. However, this does not affect all patients, and must not be misdiagnosed in those patients who have severe motor impairment and are simply unable to express themselves due to a lack of speech.

4.3 Psychiatric Features

Psychiatric symptoms are common in both prodromal and manifest HD, affecting 33–76 % of patients (van Duijn et al. 2007) and occur as part of the underlying disease process rather than simply as a response to the diagnosis. These features often cause more distress and difficulty for patients and their carers than the motor symptoms.

The most common psychiatric condition is depression, followed by anxiety, neither of which relate to the stage of disease (Craufurd and Snowden 2002). Symptoms of depression may be obscured or wrongly attributed to known features of the disease such as weight loss and sleep disturbance but it is important to recognize the condition as treatment is available and effective. A survey of 2835 patients with HD found that 40 % were suffering from depression at the time, and 50 % had sought help for depression in the past (Paulsen et al. 2005).

Suicide is the second most common cause of death in patients with HD (Lanska et al. 1988). In a separate study of 4171 patients, 10 % had made a previous attempt at suicide, and 17.5 % had had suicidal thoughts. Suicidal ideation peaks when premanifest individuals just start to display symptoms, and then again in more advanced disease when loss of independence and functioning occurs (Paulsen et al. 2005). Therefore, it is vital to enquire about suicidal ideation during assessment. Risk factors for suicide in HD include depression and impulsivity (Craufurd and Snowden 2002), but not all patients who make an attempt have depression (Lipe et al. 1993), and some patients feel that suicide is a rational response to their impending loss of independence.

Patients also develop obsessive, compulsive thoughts and behaviors (Paulsen et al. 2001). These include obsessions related to others (e.g. thoughts of infidelity), those related to themselves (e.g. fixations on bladder or bowel function) and ritualistic behaviors (with repetitive routines).

Apathy is common, and characterized by a loss of interest and passive behavior. It can be difficult to distinguish from depression but *is* related to disease stage. Often the difficulty is in initiating activities, and once patients have started on an activity they are able to participate fully.

Patients can sometimes develop irritability and aggression; rarely, this manifests in physical violence. Psychosis (paranoid thoughts and acoustic hallucinations) is a less common feature, seen in later disease stage (Rosenblatt and Leroi 2000). Hyper- and hyposexuality can be a problem in early and late HD, respectively.

4.4 Other Neurological Symptoms

In addition to the triad of movement, cognitive and psychiatric disturbances, patients also exhibit problems with communication, swallowing, and sleep disturbance.

Communication difficulties arise from a combination of dysarthria (caused by incoordination of the orofacial muscles and tongue), cognitive symptoms such as word finding difficulties, and the inability to structure speech appropriately. Patients who have developed the severe rigidity and akinesia seen in advanced HD, may be rendered completely anarthric (mute).

Likewise, swallowing problems arise from a combination of motor (incoordination of oral and pharyngeal muscles) and cognitive impairment. This leads to

increased risk of aspiration. Ultimately, patients may need to establish alternative routes for enteral feeding.

Sleep disturbance is commonly mentioned by patients with HD, and is a cause of significant distress (Videnovic et al. 2009). Insomnia may be secondary to low mood, anxiety, or chorea at night; however, primary sleep disturbance due to presumed dysfunction of circadian rhythms is also recognized. It is important to try and address the cause of insomnia so that treatment may be directed appropriately.

4.5 The Peripheral Phenotype of Huntington's Disease

Huntingtin protein is expressed by all cells in the body, and not only in the nervous system. It is unsurprising therefore, that a range of systemic features are also seen in HD (van der Burg et al. 2009). Blood plasma samples taken from patients with HD show increased levels of IL-6 and IL-8, thus providing evidence for widespread immune activation (Björkqvist et al. 2008). This may contribute to several of the peripheral features described below.

Profound weight loss occurs, greater than that seen in other hyperkinetic disorders. This cannot be explained simply by the difficulties associated with feeding and loss of swallow/manual dexterity, but is thought to be secondary to an underlying catabolic state which occurs as part of the disease process. Often this begins in the prodromal phase of the disease. Patients who have a higher body mass index at disease onset, tend to have a slower rate of progression (Myers et al. 1991).

Skeletal muscle atrophy, despite muscle hyperactivity secondary to chorea, is observed. Cardiac failure is also seen in 30 % of patients (compared to 2 % in age-matched controls) and is a cause of death in HD (Lanska et al. 1988).

Endocrine dysfunction including impaired glucose tolerance and hypothyroidism (reduced T3 levels) is often found in patients. Testicular atrophy, with reduced numbers of germ cells and abnormal seminiferous tubules can be found. Fertility remains unaffected, although men have reduced levels of testosterone. Osteoporosis may also be a part of the peripheral phenotype (van der Burg et al. 2009).

It is important to specifically assess these non-neurological features when reviewing patients in clinic as they can significantly reduce the quality of life (QoL) in HD and may contribute to an early death.

4.6 Juvenile Huntington's Disease

This is characterized by age of onset before the age of 20, and accounts for 6–10 % of all diagnosed HD (Shoulson and Chase 1975). Patients develop rigidity, bradykinesia, and akinesia right from the outset, rather than the chorea that is seen in

Table 1 The Shoulson-Fahn staging system

Stage of disease	Engagement in occupation	Capacity to handle financial affairs	Capacity to manage domestic responsibilities	Capacity to perform activities of daily living	Care can be provided at…
I	Usual level	Full	Full	Full	Home
II	Lower level	Requires slight assistance	Full	Full	Home
III	Marginal	Requires major assistance	Impaired	Mildly impaired	Home
IV	Unable	Unable	Unable	Moderately impaired	Home or extended care facility
V	Unable	Unable	Unable	Severely impaired	Total care facility

adults. Dystonic posturing is also a feature. The first outward signs of disease may manifest as learning difficulties and behavior disturbance whilst at school. Seizures are also present in 30–50 % of patients (Kremer 2002). Generally, these patients have greater than 50 CAG repeats (Andrew et al. 1993) and as mentioned previously, in 90 % of cases paternal inheritance is observed (Barbeau 1970).

The rigid variant of HD is also known as the akinetic-rigid or Westphal variant, and though usually seen in Juvenile HD it also rarely occurs in adults.

5 Disease Progression

From the time of diagnosis symptoms progress over 15–20 years. Assessment scales exist that can be used to quantify disease progression. This is essential for research purposes and also can be useful clinically in guiding interventions such as starting medication or arranging nursing home care. One of the earliest was the Shoulson-Fahn capability scale described in 1979 (Shoulson and Fahn 1979), which divides the disease into five stages and is summarized in Table 1.

Features of this were later incorporated into the Unified Huntington's Disease Rating Scale (UHDRS), which was devised by the Huntington's Study Group (Huntington Study Group 1996). The UHDRS has four components. These are the motor score (comprised of tests for oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability), cognitive tests (assessed by the digit symbols test, Stroop test, and verbal fluency), behavioral/psychiatric assessment (with specific enquiry regarding low mood, guilt, anxiety, suicidal thoughts, aggression, irritable behavior, obsessions, compulsions, delusions, and hallucinations), and a functional capacity assessment [including the total functional capacity (TFC) score]. The motor score of the UHDRS is a commonly used tool in clinic, and is helpful in objectively monitoring motor progression in a clinical setting.

Table 2 The total functional capacity score and its relationship to Shoulson-Fahn stages and clinical descriptors

Descriptor	TFC	Stage
Early	11–13	I
	7–10	II
Moderate or mid	4–6	III
Advanced or late	1–3	IV
	0	V

Giving patients a diagnosis of manifest HD has important implications for their employment, insurance policies and driving, and can have a significant psychological impact on the patient and their family and carers; premature or delayed diagnosis can therefore create problems. Once a diagnosis of manifest HD has been made, the TFC is used to define the disease stage. The TFC scale makes an assessment of the patient's ability to work, complete household finances, chores and ADLs, and what level of care they need and gives an overall combined score from 13 (independent) to 0 (fully dependent). The TFC score relates to the Shoulson-Fahn stage as detailed in Table 2, but when talking to patients and their carers, descriptive terms such as early/moderate or late are often more useful.

A deeper understanding of the natural history of HD may refine the way that we define manifest disease and monitor disease progression (Loy and McCusker 2013; Biglan et al. 2013). This is currently an area of intensive clinical research (see below).

6 Diagnosis and Investigations

The diagnosis is based on the clinical findings in association with a positive family history. Genetic testing allows us to determine the CAG repeat length in individual patients, which confirms the diagnosis. A positive test result has enormous implications not just for the patient, but also for their entire family. Patients should be made aware of this before sending blood for testing and written informed consent for the test must be given.

Neither neuroimaging nor CSF studies are useful in the diagnosis of HD. They are sometimes carried out with patients' express consent as part of ongoing research studies, or on occasion may be useful in excluding other causes of chorea (Wild and Tabrizi 2007).

In those patients who present with chorea in the absence of other cognitive and psychiatric signs, and without a positive family history, the differential diagnosis is wide (Table 3). Chorea secondary to general medical causes such as drugs or systemic illness must be considered and excluded (Roos 2010).

Approximately 1 % of patients who have a history and signs consistent with HD and who are genetically tested return a negative result. These diseases are

Table 3 The differential diagnosis of chorea, including drug induced, systemic and hereditary causes

The differential diagnosis of chorea	
Drug induced	Neuroleptics
	Oral contraceptives
	Anti-epileptics (phenytoin, carbamazepine, valproate, gabapentin)
	Levodopa and dopamine agonists
	Cocaine and amphetamines
Systemic illness	Systemic lupus erythematosus
	Thyrotoxicosis
	Polycythaemia rubra vera
	Hyperglycaemia
	Paraneoplastic
	Infective—HIV and variant Creutzfeldt-Jakob disease
	Post-infective—Sydenham's chorea, herpes simplex encephalitis
	Focal striatal pathology—stroke, space-occupying lesion
Hereditary	Benign hereditary chorea
	Wilson's disease
	Mitochondrial disorders
	Ataxia Telangiectasia
	Lysosomal storage disorders
	Amino acid disorders
	All causes listed in Table 4

known as HD phenocopies (Wild et al. 2008). Possible underlying causes of HD phenocopies are listed in Table 4. For a small proportion of patients, the genetic diagnosis remains as yet unknown. Further research on the phenocopy syndromes may offer insights into the pathogenesis of HD.

7 Management

The management of HD requires a multidisciplinary approach involving neurologists, psychiatrists, general practitioners, physiotherapists, occupational therapists, speech and language therapists, dieticians, and nurse specialists. Referral to a specialist HD clinic is recommended, as these clinics will have developed expertise in managing the condition from many different approaches and will include many of the healthcare professionals mentioned above (Novak and Tabrizi 2010). In addition, HD clinics are able to co-ordinate trials and other research studies, and recruit potential patients when appropriate. As well as being essential in expanding our knowledge of HD and potentially finding better treatments, patients generally find it psychologically beneficial to take part in research. Support from local teams in the community is vital.

Table 4 Diseases that can manifest as Huntington's disease phenocopies with their corresponding genetic cause

Disease	Mutation
Huntington's disease like syndrome (HDL) 1	PRNP—octapeptide insertion in gene encoding prion protein
HDL2	JPH3—triplet repeat expansion in gene encoding junctophilin-3
HDL3	Causative mutation as yet unknown
Spinocerebellar ataxia (SCA) 17 (HDL4)	TBP—triplet repeat expansion in gene encoding TATA-box binding protein
SCA1/2/3	ATXN 1/2/3—triplet repeat expansion in gene encoding Ataxin-1/2/3, respectively
Dentatorubral-pallidoluysian atrophy (DRPLA)	ATN1—triplet repeat expansion in gene encoding atrophin-1
Chorea-acanthocytosis	VPS13A—mutation in gene encoding chorein
McLeod Syndrome	XK—mutation in XK gene on X-chromosome, encoding a supporting protein for Kell antigen on surface of red blood cell
Neuroferritinopathy	FTL—mutation in gene encoding ferritin light chain
Neurodegeneration with brain iron accumulation (NBIA) or Pantothenate-kinase associated Neurodegeneration (PKAN)	PANK2—mutation in gene encoding pantothenate kinase 2
Inherited prion disease	PRNP—mutations in gene encoding prion protein
Friedrich's ataxia	FXN—triplet repeat expansion in gene encoding frataxin

The focus is on symptomatic treatment and on optimizing function, as currently there are no disease-modifying treatments available (Mason and Barker 2009; Bonelli and Hofmann 2007). There is however much research in this field and trials of treatments that potentially alter the course of the disease are underway. This is covered in more detail in a later chapter, and we will focus here on current management.

7.1 Drug Treatments

7.1.1 Movement Disorder

In the early stages, chorea often does not trouble the patient and therefore may not require treatment. As the disease progresses and patients start to have impaired manual dexterity or are at increased risk of falling, drug treatment should be considered. The first-line choice is the dopamine depleting agent tetrabenazine—though it may not completely abolish the excessive movements, randomized

controlled trials have shown that it does reduce choreic movements (Huntington Study Group 2006). Unfortunately, it has been shown to exacerbate or trigger psychiatric symptoms such as depression, which are common in the HD population. Therefore, it is critical to establish a psychiatric history before prescribing this drug.

Tetrabenazine requires a cytochrome P450 2D6 for its metabolism, and this enzyme is inhibited by drugs such as paroxetine and fluoxetine. Thus, the clearance of tetrabenazine would be reduced in this case and serum levels would be raised. Non-inhibitory alternatives such as citalopram or sertraline should be used instead if required (Guay 2010).

For patients with psychiatric comorbidity, or for those who have found tetrabenazine ineffective, the atypical neuroleptic olanzapine may be used. This causes side effects of increased appetite and weight gain, which may actually be useful for HD patients. In addition, it may help with psychiatric symptoms such as agitation, irritability, and anxiety. Caution is needed in patients who suffer from diabetes and regular blood glucose monitoring is required. Furthermore, an ECG should be reviewed prior to starting olanzapine, as on rare occasions the drug causes prolongation of the QT interval. Side effects also include parkinsonism, tardive dyskinesia, sedation, and raised triglycerides.

Other atypical neuroleptics that are prescribed for treatment of chorea are risperidone (which has less effect on appetite) and quetiapine (which has less effect on blood glucose). Both olanzapine and risperidone have been shown to be associated with an increased stroke risk in elderly patients with dementia (Ballard and Howard 2006), so it is important to enquire about other cerebrovascular risk factors prior to starting these drugs.

Older typical neuroleptics such as haloperidol and sulpiride may also be used but carry a greater side effect profile with more parkinsonism, akathisia (an uncomfortable internal sense of restlessness), and tardive dyskinesia. Tardive dyskinesia is a particular concern in HD as it can be difficult to detect in the presence of an existing movement disorder. All neuroleptic drugs carry the risk of neuroleptic malignant syndrome (NMS), but this risk is greater for typical neuroleptics as compared to atypicals. NMS is characterized by the acute onset of delirium, fevers, and rigidity with raised leukocytes and creatine kinase. Though it is rare, it can be life threatening and patients and their carers should be warned about this and advised to seek emergency medical help if any of the above develop whilst taking these drugs. A general principle for all neuroleptic drugs is to start at the lowest dose and titrate up gradually as needed.

When chorea is combined with dystonia, myoclonus, rigidity or spasticity, clonazepam (a benzodiazepine) is useful. Unfortunately it may exacerbate any underlying cognitive impairment, cause sedation and if stopped suddenly withdrawal seizures may occur. Anticonvulsants such as sodium valproate or levetiracetam can be used if myoclonus alone is a significant symptom.

As the disease progresses hyperkinetic movements decline and medications need to be adjusted accordingly, hence the need for regular assessment. Tetrabenazine can be weaned off and stopped, and drugs such as baclofen or tizanidine

may be introduced to address issues of spasticity and rigidity. Injections of botulinum toxin may also be effective in providing symptomatic relief from muscle spasm, and its effects can last for several months before requiring repeat injection. It must however be administered by a specifically trained individual as it can cause unwanted paralysis of muscle groups near to the injection site. For young onset HD a trial of levodopa can be considered if symptoms of rigidity and akinesia are a problem from the outset. A summary of these medications is shown in Table 5.

7.1.2 Psychiatric Symptoms

If features of depression are present then they often respond well to standard antidepressants such as selective serotonin reuptake inhibitors (SSRIs) in the first instance. Citalopram is generally used as first-line treatment; stimulating SSRIs such as fluoxetine can cause hyperstimulation and exacerbate anxiety therefore caution is required. A sedating antidepressant such as mirtazapine, taken at night, is helpful if insomnia is also a problem. Cognitive behavioral therapy (CBT) also plays a role for well-selected patients. Non-stimulating SSRIs may also help with anxiety; occasionally buspirone or benzodiazepines are also used for this.

It is essential to enquire about suicidal thoughts as patients with HD have a high risk of suicide. Psychotic symptoms (though rare) can be addressed with neuroleptic drugs such as olanzapine, which may also help with irritability and aggression. As well as avoiding situations which trigger outbursts, short term use of a benzodiazepine such as clonazepam can be useful for this. Table 6 summarizes some of the drugs that are used in the treatment of psychiatric symptoms.

The choice of drug prescribed should be based on the presence of concurrent symptoms. For example in the case of obsessive–compulsive behaviors or perseveration, neuroleptics may be useful if agitation is present, or alternatively an antidepressant if low mood is a problem. In patients with no or minimal cognitive impairment, CBT can also be useful.

Overall, it is evident that the medications prescribed must be carefully monitored as different symptoms develop and become more or less problematic throughout the disease. The risk of side effects of all of the drugs mentioned must be carefully balanced against the potential benefits they may have.

7.2 Non-Drug Treatments

The management of HD goes far beyond drug prescribing for individual symptoms. Instead, a holistic approach involving many different healthcare professionals is required. Physiotherapists play a vital role in helping to improve gait and balance, and assessment for walking aids or wheelchairs when necessary. In addition, weighted wrist and ankle bands can be provided to dampen distal choreiform movements in the early phase of the disease. Occupational therapists are