Premanifest and Early Huntington's Disease

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Abstract

The traditional view that individuals carrying an expanded HD gene undergo 'phenoconversion', a stochastic event that takes them from symptom-free to symptomatic, is now disputed among clinicians, HD researchers and patient and family advocates alike. Disease onset is officially declared when neurological abnormalities 'unequivocally' due to HD are diagnosed, but subjective symptoms and objective signs emerge gradually and it is more helpful to consider and openly discuss a 'prodromal' period, often as long as ten years, which can provide a helpful framework for discussion and management. Considerable progress has been made in defining the neurobiological processes that underlie the development of HD in humans and measures that can predict this for the purpose of conducting clinical trials, but these measures have not yet been validated sufficiently to make them useful in the clinical setting. We discuss the multidisciplinary care of patients with premanifest, prodromal and early manifest HD.

Keywords

- Premanifest HD
- Early HD
- Prodromal HD
- Clinical management
- Biomarkers

1. Introduction

This chapter deals with the clinical features, management and clinically relevant research findings in premanifest and early Huntington's disease. A chapter dedicated to these disease stages is included in this volume for the first time because research into the neurobiology of HD in human subjects has improved our understanding to an extent that is clinically useful in defining and managing patients

undergoing the transition from symptom-free to manifest HD. Moreover, this group of patients is the main focus for current and future trials of novel therapeutics aimed at slowing the progression of HD.

The early stage of Huntington's disease is a time when symptoms, signs and, most importantly, the ability to function in everyday life can change rapidly and be challenging for patients, carers and healthcare professionals; yet it also affords perhaps the greatest opportunity for amelioration and even improvement with the appropriate multidisciplinary care.

The years preceding early disease, meanwhile, are a difficult area for families and clinicians alike. It is increasingly agreed that a 'prodrome', often lasting many years, of symptoms, signs and sub-clinical abnormalities frequently precedes the emergence of more evident disease features. Defining the features of this prodrome is seen by many as a key fundamental step towards the development of therapeutics aimed at preventing the disease; but also raises the possibility of bringing forward the age when the disease has 'begun' - or even defining HD as a lifelong continuum – seen by some as undesirable or stigmatising. The main aim of this chapter is to describe the current state of our understanding of the years before and after the first overt disease signs are seen; but in view of these contentions, we begin with a discussion of some important definitions.

2. Definitions and controversies

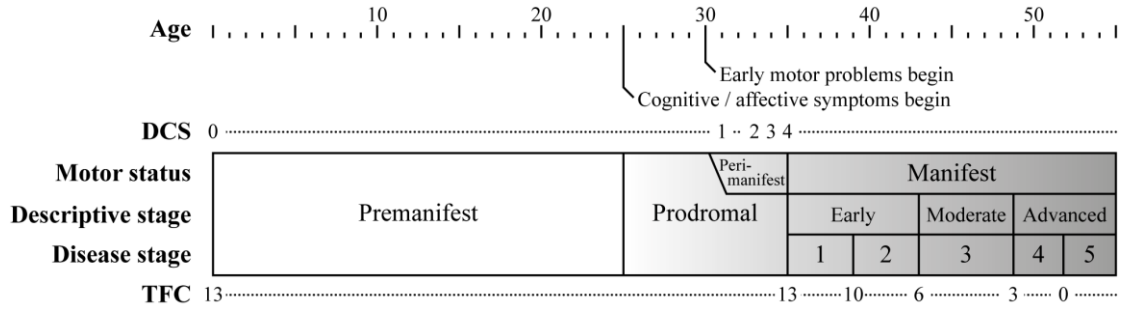

Figure 1 Representation of the lifespan of a single HD expansion carrier, officially diagnosed as having manifest disease (DCS 4) at 35, preceded by ~10 years of 'prodromal' cognitive / affective complaints and 5 years of soft motor 'perimanifest' problems. Note the dependency of motor status on DCS, and disease stage on TFC. Though this basic pattern is commonly seen, HD is above all highly variable and unpredictable. DCS, diagnostic confidence score; TFC, total functional capacity.

2.1. Motor onset

For both research and clinical purposes, Huntington's disease has historically been modelled as having a moment of motor 'onset'. We have not used the term 'phenoconversion' as this implies an 'all or nothing event', which is clearly not the case as a person progresses from the prodromal to the early phases of the disease. This is depicted in Figure 1 alongside the various means used to divide the

lifespan of a person affected by HD. By consensus, onset is defined as the point when a person who carries a CAG-expanded *HTT* allele develops "the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity)" (The Huntington Study Group, 1996; Hogarth et al., 2005).

The Unified Huntington's Disease Rating Scale (Shoulson and Fahn, 1979; Shoulson, 1981; The Huntington Study Group, 1996), is used for both research purposes and as a guide to clinical decision-making, particularly around diagnosing motor onset. It contains a 'diagnostic confidence score' (DCS) subscale (see Table 1), which scores a subject from 0 (no motor abnormalities suggestive of Huntington's disease) to 4 (motor abnormalities ≥99% likely to be due to HD). A person who attains a score of 4 on this scale, when assessed by an expert rater, is said to have undergone 'motor onset'.

Description	**Score**
Normal (no abnormalities)	0
Non-specific motor abnormalities (less than 50 % confidence)	1
Motor abnormalities that may be signs of HD (50 - 89 % confidence)	2
Motor abnormalities that are likely signs of HD (90 - 98 % confidence)	3
Motor abnormalities that are unequivocal signs of HD (≥ 99 % confidence)	4

Table 1 UHDRS motor diagnostic confidence score (DCS) (The Huntington Study Group, 1996)

The advantage of this model is that, amid the considerable clinical phenotypic heterogeneity of the disease, 'motor onset' as diagnosed according to this definition has repeatedly emerged as one of the more robust and consistently agreed disease features. Motor onset has relatively high inter-rater agreement: in one study of 75 clinicians shown video recordings of HD subjects, the proportion of agreement (expressed as κ scores) was 0.67 for DCS values of 4. However, for lesser scores agreement was poor — only 0.32 (Hogarth et al., 2005). The practical value of the intermediate scores 1, 2 and 3 is questionable, and it may be more helpful to consider whether an individual has equivocal abnormalities or unequivocal abnormalities without the rather artificial 'quantification' of confidence as a percentage.

Thus, motor onset is of value for establishing entry and exclusion criteria for clinical studies and trials, and as a 'hard' endpoint for studies of genetic or environmental modifiers of the disease. For carriers of an expanded HD gene, too, the concept of motor onset can be of value: it is reassuring to hear that the disease has not officially 'begun', even if a person may be experiencing 'soft' symptoms; and when the moment comes for a physician to confirm that motor onset has unequivocally occurred, it can be a trigger for important life decisions around work, care, future planning and so on.

However, if adhered to rigidly, the concept of 'motor onset', may amount to a false dichotomy with the potential to adversely affect understanding of the disease and clinical care. It would be wrong to infer that there is a day, month or even year when a dormant disease process begins and motor signs appear, from which point a person's health is expected to decline linearly. As we shall see, evidence from human observational studies and animal models now substantiate the long-held assertions of HD family members that subtle changes invariably begin several years before motor problems become apparent, implying that pathogenic processes begin even earlier. Some have even suggested that the expanded HD gene has effects on development in humans, though this is not yet clearly established (Nopoulos et al., 2011; Lee et al., 2012).

One unfortunate side-effect of the notion of stochastic 'onset' is the possible impression that until the diagnosis of motor onset, there is no possibility of HD-related symptomatology that could be amenable to treatment. In our experience this palpably false misconception does remain prevalent among primary care physicians and even neurologists.

Despite these reservations, motor onset remains a widely-used event in both clinical and research settings because of its intuitiveness and inter-rater reliability. However, an increasing awareness and acceptance that 'disease onset' as currently defined is really a process that occurs gradually over years or even decades, is enlightening the approach of researchers and clinicians.

2.2. Premanifest, prodromal and perimanifest definitions

The *HTT* gene is expressed through early development, and it has been suggested that Huntington's disease may be considered a lifelong illness, with both developmental and degenerative aspects. Mouse embryos lacking either allele do not survive to birth (Duyao et al., 1995; Nasir et al., 1995; Zeitlin et al., 1995), implying that the HD gene is expressed from early development. Indeed, CAG repeats in the highly expanded range cause onset of HD adolescence or childhood (Chapter 4) with onset as young as two years of age having been reported (The Huntington's Disease Collaborative Research Group, 1993).

Strictly speaking, 'premanifest' is not synonymous with 'presymptomatic' or 'asymptomatic'. *Symptoms*, such as low mood, are experienced objectively but cannot be observed, while disease *signs* like chorea are apparent on examination. Signs and symptoms often go hand-in-hand, but this is not always the case. Some HD expansion carriers have clear motor abnormalities but report no symptoms; more commonly, subjective complaints of cognitive and affective symptoms precede motor onset.

Patients with symptoms but not unequivocal signs, or soft motor signs only, are sometimes said to be in a **prodromal** stage of HD (e.g. Harrington et al., 2012). By definition, prodromal HD cannot be diagnosed beyond reasonable doubt, as per the standard for manifest HD; rather it must necessarily be judged and treated on the balance of clinical probability. Symptoms of prodromal HD are increasingly

recognised as requiring diagnosis, discussion and management (Novak and Tabrizi, 2010; Ross and Tabrizi, 2011).

The term 'perimanifest' (or 'cusp') is sometimes applied to patients with prodromal HD who are felt by their clinician, on the balance of symptoms and 'soft' motor signs, to be likely to progress to a formal diagnosis of manifest HD in the future (Tabrizi et al., 2012). Perimanifest patients have DCS values that rise from one to three (bearing in mind the caveats above) with a UHDRS total motor score >5 and often reaching low double digits, before the DCS is increased to 4 and motor onset is said formally to have occurred (Tabrizi et al., 2009). Motor abnormalities of this magnitude are subtle: in contrast, patients with manifest HD often have total motor scores in excess of 50. It should be noted that the idea of 'perimanifest' HD is not recognised by all authorities, on the basis that minor motor abnormalities occurring in prodromal HD do not require a special designation in themselves. However, a growing body of evidence does support a clinical utility for detecting and managing these subtle motor phenomena and for a value in predicting formal diagnosis of motor onset, and we do favour the judicious use of this term.

2.3. What is early HD?

In contrast, early Huntington's disease is relatively easy to define. After the onset of motor abnormalities (in other words, once the DCS reaches 4), it is function, rather than motor signs, that determines disease stage (Shoulson and Fahn, 1979; Shoulson, 1981). The UHDRS total functional capacity (TFC) scale assesses a person with HD in terms of ability to work, complete household finances, chores and activities of daily living, and what level of care they need. The scale ranges from 0 (fully dependent for all care) to 13 (fully independent); see Chapter 2, Table 1B. Based on the TFC, five disease stages (often referred to as Shoulson-Fahn stages) are defined (see Figure 1 and Table 2).

TFC	Stage	Descriptor
11-13	1	Early
7-10	2	
4-6	3	Moderate or mid
1-3	4	Advanced or late
0	5	

Table 2 Huntington's disease stages (Shoulson and Fahn, 1979; Shoulson, 1981)

For many purposes, the five numeric stages are rather too granular and lack obvious intrinsic meaning for patients, family members and professionals. Thus, the informal descriptors 'early', 'moderate' (or 'mid-stage') and advanced (or 'end-stage') are often used, corresponding to Shoulson-Fahn stages 1-2 (early), 3 (moderate), and 4-5 (advanced), as shown in Figure 1 and Table 2.

One value of these stages is that, broadly speaking, they relate to meaningful situations functionally. Stage 1 patients are generally still able to work, perhaps with some difficulty or adaptations. During stage 2, many patients find they must retire from work and, though able to walk, this usually becomes

somewhat impaired along with a need for assistance with household chores and finances. In stage 3, these tasks are generally surrendered to others and walking usually requires assistance from aids or a wheelchair is used. Stages 4 and 5 are characterised by significant and total dependence on external care respectively (Shoulson and Fahn, 1979).

The system of defining disease onset as the emergence of unequivocal motor signs, and the division of the disease into broad stages in this manner is widely used and undeniably provides a useful framework for managing most patients clinically, as well as characterising them for the purpose of clinical research studies. But, in view of the inherent variability of the disease and the controversies and reservations mentioned above, it is important always to bear in mind that each patient should be considered individually and in terms of the totality of their symptoms, signs and function.

3. Premanifest HD

The premanifest phase of an HD expansion carrier's life extends from birth to the beginning of the prodromal phase, defined by the development of subjective symptoms or objective neurological abnormalities. Though it may seem unusual to be describing the 'clinical' features of the premanifest stage of an illness, hopefully the preceding discussion regarding prodromal HD establishes the need to do so. Even at the stage where a person who carries an expanded HD allele has no subjective symptoms or objective signs, there is still a role for the involvement of a specialist clinical team to address problems and concerns relating to HD. As time goes on, most patients develop symptoms which may represent prodromal HD, which is to say symptoms due to HD prior to formal diagnosis of motor onset. Primary care and specialist clinicians share a role in diagnosis, management and support through these phases.

3.1. Predicting onset

As discussed in detail elsewhere in this volume, the only known determinant of age at onset in HD is the length of the larger CAG repeat in the HD gene (Andrew et al., 1993; Duyao et al., 1993; Snell et al., 1993), and repeat length is now increasingly accepted as having an influence on rate of progression once manifest disease begins (Mahant et al., 2003; Ravina et al., 2008).

Though CAG repeat length is a relatively strong predictor of mean age at onset when applied to large cohorts, it is of very limited value in giving useful information concerning an individual, partly because of the inherent variability of HD because of the influence of other genes and environmental modifiers of disease; and especially because the majority of expansion-carriers have repeat counts in the 40-50 range where variability is greatest (Langbehn et al., 2004).

A useful recent development is the conditional onset probability model developed by Langbehn and colleagues, based on a large multi-population cohort of nearly 3,000 individuals. Rather than simply predicting an individual's likely age at onset from birth, based purely on the CAG repeat count, it

makes use of additional clinical information: that an individual has survived to their current age without developing motor signs, to modify the future onset probability. For example, an individual with a repeat length of 44 would be predicted, at birth, to have a 77% probability of onset by the age of 50 years; but if the same individual remained disease-free at 45, their conditional probability of onset by the age of 50 would be reduced to 53%, because of the information about their genotype-phenotype concordance encoded in 45 years' disease-free survival. Thus is becomes possible to predict for a given subject the probability that they will remain disease-free for a specified number of years – conventionally five. It can also be used to predict, for a given individual, the number of years of disease-free life that must elapse before they reach a conditional onset probability of interest (conventionally 50 or 60%) (Langbehn et al., 2004).

It should be reiterated, however, that this more sophisticated model does not change the basic heterogeneity of HD, nor the tendency of most pathogenic expansions to lie in the most unpredictable range (Langbehn et al., 2004), nor the fact that 'onset' remains a convenient yet artificial construct we impose on a continuous disease process. A 50% probability of onset represents anything but certainty, and the model cannot supply reliable estimates for the very high probabilities we would like to be able to predict.

Thus, though we can better model HD at a population level, for the purpose of cohort-based research, it remains the case that for the vast majority of individuals, CAG repeat length cannot provide useful information about when symptoms will begin or what form they will take. Most centres now quantify the size of both alleles during the genetic testing process and it is common for those undergoing testing to enquire about the precise CAG count. Some centres still decline the information because of its limited value and the potential for misinformation. Most are willing to inform the patient of the CAG count on request. If this is to be done, it is essential that a clear explanation of the limitations of the information be given (Novak and Tabrizi, 2010).

3.2. Asymptomatic expansion carriers

A truly asymptomatic individual bearing a CAG-expanded HD allele has, by definition, no signs or symptoms that can be ascribed to the pathobiology of HD. Nonetheless, because of its singularly long reach, the disease may still cause significant problems in the lives of such people. We do not here address the issue of predictive genetic testing in HD, which is covered in Chapter 8, but which represents a significant dilemma and life choice for anyone who knows they are at risk. Equally, the earliest problems due to HD invariably arise as a result of what may be referred to as the 'HD environment' – that is, the effect on young people of growing up in the chaotic home situation that HD often produces. These issues can have significant effects on development, schooling and psychological and physical wellbeing (Forrest Keenan et al., 2007) but, since they affect those with and without an expanded HD allele, cannot be considered 'asymptomatic' effects of HD. We therefore focus on the

HD-related problems of individuals who have undergone a positive predictive genetic test for the HD expansion.

Many asymptomatic individuals carrying an expanded HD allele seek and require no attention from healthcare professionals. Indeed it is common for an individual to undergo genetic counselling, testing and post-test support in a multidisciplinary HD clinic, then not return for years or decades. Many such individuals are fully capable of living full lives, working, forming families and planning ahead for later life when disease manifestations are anticipated. However, in our practice we recognise that a significant proportion of premanifest expansion-carriers do experience problems relating to knowledge of their genetic destiny, for which the multi-disciplinary HD clinic is well placed to offer assessment and advice.

Many asymptomatic individuals experience the phenomenon colloquially referred to as 'symptom-hunting', though this has not been described or studied formally (e.g. Huntington's Disease Youth Organization, 2011). This refers to the natural tendency of those who know they will develop HD to infer that symptoms have begun on the basis of minor, normal occurrences such as forgetting someone's name, dropping an object, tripping or feeling short-tempered. Equally, premanifest individuals may feel entirely well but be aware, from having witnessed the illness of a relative, of the impaired insight caused by HD (Ho et al., 2006), and that an affected person may therefore be unaware that they have developed manifest disease. In both of these situations, it can be helpful for the asymptomatic individual to visit the specialist clinic infrequently – perhaps annually or biennially – in order to undergo a detailed neurological examination including the UHDRS motor scale, performed by an experienced clinician, and be told that they remain free from objective disease signs. In our experience, many patients find this routine sufficiently reassuring to enable them to continue functioning effectively in the interim.

If there is any doubt as to whether any mild cognitive symptoms described have an organic basis, it can be helpful to obtain a formal neuropsychometric assessment administered by a neuropsychologist with experience of HD. This can both provide reassurance and serve as a baseline for future assessments. Low mood, depression and anxiety, which are of course common primary phenomena in the general population, can occur in asymptomatic individuals, independently of the organic neuropsychiatric problems caused by HD. Such individuals are prone to developing primary psychiatric problems because of the 'HD environment' combined with knowledge of their own genetic status (Larsson et al., 2006). A formal neuropsychiatric assessment can be of value for diagnosis and management here, though it can be extremely difficult to distinguish between primary psychiatric problems and a neuropsychiatric presentation of HD. The complete absence of cognitive, motor and oculomotor findings is reassuring in this setting; neuropsychometric testing is again helpful here.

Advances in neuroimaging, cognitive assessments and quantitative motor techniques have improved our understanding of the early pathobiology of HD, and our ability to detect disease-related changes in

premanifest human subjects (see ‘Detecting the earliest disease changes’ below). However, there is presently no clinically proven role for any of these novel modalities in enhancing our ability to predict or diagnose the onset of HD symptoms or signs in individual cases.

A further role for the HD multidisciplinary clinic for asymptomatic individuals is in offering advice about planning for the future. It is generally agreed that issues like life insurance, constructing an advance directive or living will (formalising decisions around residential care, gastrostomy feeding, cardiopulmonary resuscitation and end-of-life care) and arranging power of attorney are best dealt with by the whole family, as early as possible and ideally prior to symptom onset. They then represent one less source of concern once symptoms begin, though can of course be revisited later. Counselling around these issues can be offered jointly by the specialist clinic, the primary care team and the HD lay organisations.

Fertility options and assisted reproduction for asymptomatic individuals are discussed in detail in Chapter 8 but are an area where the specialist clinic can again be a useful source of reliable information. Despite genetic counselling, many asymptomatic people are unaware of the range of options available or how to access them; and some primary care teams are unwilling to refer or unaware that they may do so. In our experience it is helpful to mention reproductive options whenever an asymptomatic individual attends the specialist clinic.

A clinical research programme involving human volunteers is a feature of many specialist HD clinics, and many studies include asymptomatic individuals, who are often enthusiastic to hear about the latest research developments, for obvious reasons. Notwithstanding the increasing availability of reliable information about HD research online (e.g. HDBuzz.net), we find that many people also value the opportunity to interact directly with experts who are involved with, or apprised of the latest research. In our view, such exchanges are also valuable when it comes to educating and engaging potential volunteers in preparation for future trials of symptom-postponing treatments (Wild and Carroll, 2012).

3.3. The prodromal phase

The prodromal phase of HD, when subjects experience mild and often progressive symptoms of HD before motor onset has been formally diagnosed, is a difficult time for all concerned. All the above problems that can occur in premanifest HD are still possible in this phase, but it is characterised additionally by the development of symptoms too subtle or non-specific to be sufficient at the time to allow a formal diagnosis of motor onset. Thus, to the worry of experiencing symptoms is added the uncertainty of whether those symptoms reflect the earliest evidence of future decline. Function may appear well-preserved during prodromal HD, but may be achieved only through additional effort, itself an additional source of stress. The TFC scale, the most commonly used functional rating scale in HD, lacks the ability to detect the effects of symptoms that make functioning more difficult without actually producing a marked deterioration in overall ability. Subtle ‘perimanifest’ motor signs may emerge, usually later in the prodromal phase (Tabrizi et al., 2012). Again, these may cause functional

impairment, a need for more effort with motor tasks, or avoidance of activities, even before the DCS reaches 4 and motor onset is confirmed.

In recent years, a clearer and more unified description of prodromal HD has emerged, thanks to large studies of premanifest volunteers. PREDICT-HD followed a large cohort of premanifest expansion carriers at 32 sites from 2001 and applied motor examination, cognitive assessments, olfactory function assessment and MR (magnetic resonance) imaging biennially (Paulsen et al., 2008). TRACK-HD studied 366 subjects at 4 sites, including 120 premanifest expansion-carriers, using a more detailed battery including quantitative motor assessments (gait analysis, grip strength, tongue force), 3 tesla MR imaging, computerised oculomotor assessment and a cognitive battery informed by the preliminary results from PREDICT-HD (Tabrizi et al., 2009).

These large studies broadly agree that prodromal HD is reliably detectable at the group level, and the severity of its symptoms is associated with CAG repeat length and closeness to disease onset. Cognitive and motor symptoms are the most consistent features.

In terms of cognition, PREDICT-HD found mild but consistent and relatively widespread cognitive dysfunction in prodromal HD: the prominently affected domains were speed/inhibition, verbal learning/memory, attention-information integration, sensory-perceptual processing, and motor planning/speed; of these, only the latter two were predictive of motor onset (Harrington et al., 2012). TRACK-HD identified significant baseline impairments in facial emotion recognition, visual working memory and smell identification (Tabrizi et al., 2009). In neither study did longitudinal observation reveal changes in cognition in premanifest HD that could reliably be distinguished from control subjects, reflecting the need for more sensitive or challenging cognitive tests in this group (Hart et al., 2011; Tabrizi et al., 2012).

Naturally, patients with prodromal HD do not complain of defects in visual working memory or attention-information processing. Common subjective cognitive complaints in this group are relatively nonspecific and include general slowing difficulties with multi-tasking, forgetfulness and the need for increased effort to achieve tasks.

Patients in the prodromal phase are likely to experience ‘soft’ motor manifestations, perhaps causing small elevations in the UHDRS motor score and with a DCS score that gradually increases from zero towards four with subsequent examinations. Though the UHDRS motor scale remains a crude tool for diagnosing prodromal HD, a score that rises year-on-year, is probably the most reliable suggestion that motor onset is approaching. This is affirmed by the TRACK-HD and PREDICT-HD studies, both of which confirmed that such minor elevations were a robust finding, predictive of progression to early manifest HD (Biglan et al., 2009; Tabrizi et al., 2011).

Specific signs commonly held to be among the earliest motor manifestations include unconscious ‘finger-flicking’ while walking (see Wild and Tabrizi, 2007 for video clip), the Luria ‘fist-edge-palm’

motor sequencing task and postural instability (Salomonczyk et al., 2010). Assessment of oculomotor signs – which in prodromal HD may be limited to subtle saccadic delay and gaze impersistence - remains a useful adjunct to the overall clinical picture, but is rarely crucial in making a diagnostic determination.

Neuropsychiatric manifestations are a core feature of prodromal HD. Depression, anxiety, apathy and irritability are all common but of course are non-specific. Interestingly, the TRACK-HD baseline data revealed significant differences in apathy and irritability but not in affective domains, perhaps reflecting that depression and anxiety are relatively treatable, in contrast to the other derangements (Tabrizi et al., 2009). Again, the presence of these symptoms in an HD gene expansion-carrier is suggestive of prodromal HD, especially when progressive and when seen alongside the other features described here – but none can be used to make a definitive diagnosis. Treatment of these aspects can nonetheless be attempted irrespective of whether they can be ascribed definitively to HD.

From the prodromal phase onward, impairment of insight into symptoms is a feature of HD (Ho et al., 2006). Indeed, it is axiomatic that a patient who is concerned about onset has probably not yet encountered it, since the emergence of symptoms and signs is so often associated with a lack of awareness that it has occurred. Insight is discussed further below.

Despite considerable recent progress in defining the phenotype of prodromal HD (see 'Detecting the earliest disease changes' below), advanced techniques such as computerised oculomotor and quantitative motor assessment or MR imaging remain research tools with no established role in the clinical evaluation of individual patients. Thus, though a relatively distinctive prodrome of cognitive, motor and neuropsychiatric dysfunctions clearly exists in most patients before formal motor onset, the fact remains that in an individual case, it is by definition impossible to diagnose prodromal HD 'beyond reasonable doubt'.

The pitfalls here are considerable. Premature diagnosis or secure prediction of manifest HD can lead to patients' taking major life decisions such as medical retirement, only to fail to deteriorate as expected. Patients may remain convinced that they have begun to experience symptoms and be unpersuadable otherwise; for many others, the opposite situation prevails – the clinician and relatives are confident that HD-related impairment has begun, but the patient cannot or will not accept this. Finally, in the middle are cases where everyone agrees that *something* has changed but nobody can prove it definitively, less still suggest a treatment:

> *I am not as whole as I was. My thought processes have slowed down and it takes enormous self discipline to do ordinary things like getting dressed—it's exhausting. I recognised these changes in myself years before anyone else did, and it is important that other people (including healthcare professionals) just accept this—the changes don't have to be measurable. They can't reassure me that all is well but they can support me. By accepting that changes are happening, they give me permission to adapt my life at an early stage. I have changed my high powered job*

to an "ordinary" job, for example, which has taken pressure off me and allowed me to put energy into other things. The end stage of Huntington's disease will happen no matter what, but I will live most of my life before this point and I want to make the most of it.

Sue Walters, Hertfordshire (Novak and Tabrizi, 2010)

No consensus exists on the best way to deal with this uncertain situation. Some clinicians, seeing soft signs, prefer not to disclose them to the patient, unless specifically asked, because of the risk of over-interpretation or from a desire not to cause undue concern. Given what we have learned about prodromal HD in the past decade, as well as clinicians being seen increasingly as partners in patient-centred care (Taylor, 2009), in general, we favour an approach of openness and sensitivity, in which available information and suspicion is shared with patients and relatives, concerns are acknowledged without being unduly amplified, explanations are offered of why certainty is impossible. Against this backdrop, available tests (e.g. neuropsychometry) can be arranged to help clarify and monitor the evolving situation, treatment proposed for whatever symptoms may be treatable, and ongoing support and re-evaluation offered.

4. Early Huntington's disease

The general features of Huntington's disease have been well described in Chapter 2. Here we focus on those features that are common in early manifest HD – Shoulson and Fahn stages 1 and 2 – how they typically affect the patient and their family, and an approach to multidisciplinary care.

As we have seen, early Huntington's disease is defined and characterised by the presence of unequivocal motor signs of the disease, with either no functional impairment, or relatively little. But during the course of early disease, significant functional loss is inevitable (see Figure 1 and Table 2). The vast majority of patients have cognitive and/or psychiatric symptoms by the time motor onset is diagnosed (Johnson et al., 2007). Thus, the overall picture of a 'typical' early HD patient is someone with a combination of hyperkinetic involuntary movements, mild impairment of voluntary motor function, and a combination of behavioural (typically affective) and cognitive symptoms. We address these in turn, but of course in the individual they must be considered together.

4.1. Presenting features

It is difficult to be certain of the accurate proportions for the cardinal or presenting features of early HD. The historical definition implies that disease **must** begin with motor features unequivocally due to HD. At the same time, patients and clinicians alike, acknowledging the existence of prodromal HD or symptoms in the absence of signs, have in reality recognised early HD on the basis of non-motor features, whether formally or informally and whether contemporaneously or in retrospect.

In a study of 960 patients diagnosed as having undergone 'motor onset', motor abnormalities were retrospectively felt by the clinician to have been the earliest disease symptom or sign in only 56%.

Psychiatric, cognitive and multifactorial presentations were almost as common (Figure 2) (Marder et al., 2000). This heterogeneity has been borne out by subsequent, larger studies (Orth et al., 2010). In fact, many patients will develop symptoms in multiple domains in relatively quick succession, and it is unusual for a patient to enter the early stage without symptoms of some degree in the cognitive, motor and behavioural domains.

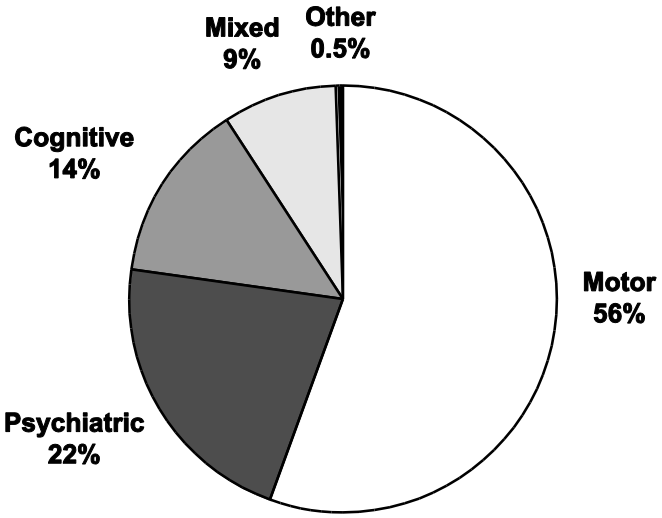

Figure 2 Initial presenting feature of HD, determined retrospectively by clinician in 960 patients with 'manifest' disease (Adapted from Marder et al., 2000).

4.2. Motor features

As with later stages of HD, a balance of involuntary hyperkinetic movement disorder and loss of voluntary control including parkinsonian features is seen in early HD. Most typical adult-onset patients experience chorea at some point during the illness, and it is particularly likely to be present in early disease, since in the later stages chorea tends to give way to dystonia, which is relatively rare in early HD. Patients who will go on to develop the parkinsonian Westphal variant of HD (Chapter 4, juvenile HD) often do nonetheless experience a degree of chorea early in the illness; but their motor phenotype is usually dominated by bradykinesia from the outset (Young et al., 1986; Thompson et al., 1988).

Chorea in early HD is usually relatively mild – low amplitude, relatively infrequent and at least partially amenable to voluntary suppression – but can progress with surprising rapidity. The chorea of early disease generally resembles an exaggerated form of 'fidgetiness' that may be seen in normal individuals. Postural adjustments, position-shifting, finger-flicking, shoulder-shrugging, eyebrow-raising and other transient facial movements such as smiling or grimacing are particularly common components of this overall fidgetiness. As the chorea progresses, it begins to exceed the range of physiological movements in both frequency and severity. Larger movements of the limbs occur in an increasingly undirected manner, though for a time these may be detected after initiation and

'converted' into directed movements like gestures or adjusting the hair (Young et al., 1986; Wild and Tabrizi, 2007).

Chorea is more likely to begin in the upper limbs than the face or lower limbs. Limb chorea is generally bilateral but often asymmetrical in early disease, even if it later usually becomes generalised and symmetrical. At all stages, but perhaps most noticeably in early disease, chorea is exacerbated by stress, anxiety, intercurrent illness, fatigue and often caffeinated drinks (Young et al., 1986; Novak and Tabrizi, 2010).

Early stage HD patients are frequently characterised by a striking lack of awareness of the severity of the hyperkinetic movement disorder, even if chorea is marked. This is a specific feature of the more general loss of insight that is characteristic of HD (Ho et al., 2006). Lack of awareness of chorea seems, at least anecdotally, disproportionate to poor insight into other features (Snowden et al., 1998). The reasons for this are not clear but it seems likely to be due to parallel deterioration of the frontal-striatal networks jointly responsible for suppressing involuntary movements, mediating awareness of movement and facilitating insight (Duff et al., 2010)

As discussed in Chapter 2, the name 'Huntington's chorea' was abandoned because of the increasing realisation that chorea, though the most obvious feature of the disease, does not occur in isolation. In early disease, thanks to its being amenable to voluntary modulation or suppression in many cases, the functional impact of chorea on gait, balance and upper limb function is surprisingly small. Chorea may nonetheless be embarrassing or inconvenient for patients and relatives (for instance, nocturnal chorea may disturb a partner's sleep). But the more functionally disabling movement disorder is the impairment of voluntary control (Shoulson, 1981; Thompson et al., 1988). This represents a variable, compound movement disorder consisting of a number of features of HD that are common in early disease, including impaired motor learning (Ghilardi et al., 2008), bradykinesia, loss of postural reflexes (Salomonczyk et al., 2010), ataxia, motor impersistence and impaired fine motor control (Young et al., 1986; Novak and Tabrizi, 2010).

The balance of these individual contributions to functional impairment of locomotion, balance and upper limb activities is variable and difficult to assess, and, contrary to their relative contributions to functional disability, the widely-used UHDRS motor scale attributes 48 points to chorea but only 32 to voluntary motor function (The Huntington Study Group, 1996). It is thus essential, in the assessment of an early HD patient, to assess voluntary motor function specifically, and enquire about its impact on functional activity, bearing in mind that this may be disproportionate to both its appearance in the clinic and the severity of the hyperkinetic movement disorder.

Speech and swallowing may be affected in early Huntington's disease, but it is relatively rare for these to be prominent or severe. Language production is generally unaffected by the cognitive effects of HD so if speech is abnormal, it is due to dysarthria resulting from the voluntary motor impairment mentioned above. Dysphagia due to disintegration of the motor control of swallowing is near-universal

from moderate stage HD onward, but in early disease swallowing problems are more likely to be disordered through behavioural dysfunction, with poor impulse control causing chewing to be incomplete and swallowing rushed. Video fluoroscopy can be very helpful in distinguishing the relative contributions of motor and behavioural dysfunction to poor swallowing (Heemskerk and Roos, 2011; Hamilton et al., 2012b).

Oculomotor dysfunction is a cardinal feature of HD, as described in Chapter 2. Like chorea, saccade initiation delay, slowing of saccades and gaze impersistence may be prominent in early HD but are more visible to the neurologist than noticeable to the patient.

4.3. Cognitive and neuropsychiatric features

Neuropsychiatric, behavioural and cognitive problems are common throughout HD. These have been described in detail in Chapter 3. Here we focus on the characteristic combination of these aspects that tend to emerge in early disease. Patients at all stages are at risk of acute psychiatric crises involving major axis symptoms such as depression, anxiety, mania and psychosis, usually set against a chronic background of affective disorder, cognitive impairment and personality change that is near-ubiquitous and tends to worsen through early and moderate disease (Paulsen et al., 2001). The picture in early HD tends to consist of a combination of low mood, anxiety, irritability, apathy and mild but widespread cognitive difficulties resulting in problems with high-level tasks (Thompson et al., 2012). The functional impact of these changes is often considerable but thankfully many symptoms in the psychiatric/behavioural domain are especially treatable in early HD (Phillips et al., 2008), while early cognitive dysfunction is at least amenable to amelioration through managing mood and anxiety and the education of patients, carers and employers (Nance et al., 2011).

The context to the cognitive and neuropsychiatric picture of early HD is particularly important. Many people will have undergone predictive testing many years earlier and anticipated an ‘official’ diagnosis of manifest HD with dread, exacerbated by witnessing the decline of relatives or caring for them. As we have seen, most people entering early manifest disease will have encountered symptoms of prodromal HD for years beforehand, including cognitive and affective problems; in many cases, because of the slow advance of these symptoms and characteristic loss of insight, the patient may be unaware of symptoms that are obvious to other family members or work colleagues. During early disease, each patient must adapt from enjoying full function to managing the slow worsening of both physical and mental problems and inevitable progressive functional impairment. This adjustment is both a cause, and a consequence, of cognitive and behavioural symptoms: fear of imperfect performance at work combines with supposed or actual additional pressure from employers to compound symptoms and accelerate functional decline.

Most patients with early HD experience low mood and many (around half at any time) become clinically depressed (Pflanz et al., 1991). A reaction to the onset of physical illness and functional impairment may explain some part of this tendency, but studies have shown that the degree of

depression in HD is greater than that accounted for by a normal grief or adjustment reaction (Mindham et al., 1985). Low mood is frequently combined with anxiety in early HD, which often focuses on work and social situations (Thompson et al., 2012). Again, a downward spiral can easily develop between poor perceived or actual performance and anxiety about work. Thankfully, depression and anxiety are treatable in many cases.

Risk of suicide or self-harm, which is elevated throughout the course of HD, is particularly an issue in early disease (Farrer, 1986; Paulsen et al., 2005). In patients with impaired insight, being informed of the onset of symptoms can come as a surprise even if the deterioration was obvious to family members or work colleagues. Combined with the tendency to depression and impulsivity, and of course the onset of function-limiting physical symptoms and the knowledge that the disease is slowly progressive, early stage disease is a high risk time (Paulsen et al., 2005). It calls for a sympathetic approach from professionals, particularly around informing the patient of the onset of manifest disease, and offering increased support to patient and family afterwards, followed by close monitoring of the neuropsychiatric state in the community and the specialty clinic. Enquiry should be made about mood, biological symptoms of depression and thoughts and intent of self-harm at each visit.

Irritability is particularly prominent and problematic in early HD, since it too is compounded by the increased stress felt by many patients struggling to retain function, and can also contribute to the deterioration of relationships in the workplace and at home, exacerbating the patient's difficulties. Apathy, though less common than in later disease, can appear in early HD, and cause great frustration to carers who may feel the patient has 'given up' (Thompson et al., 2012).

Any or all of the cognitive domains mentioned in Chapter 3 may be affected in early HD. The earliest and most prominent deficits characteristically appear in executive functioning and psychomotor function, and are manifest in the workplace where the cognitive challenge is highest. Subjectively, patients frequently report problems with concentration, attention, planning tasks and multitasking, on a background of taking longer to achieve tasks due to psychomotor slowing. Reports of memory impairment at this stage are more likely to be secondary to poor accumulation of new memories because of attentional deficits than due to a primary impairment of mnestic function (Lundervold et al., 1994). Needless to say, cognitive difficulties are exacerbated by affective disorder and vice versa, creating yet another feedback loop that can accelerate functional decline.

4.4. Other features

As described in Chapter 14, non-CNS manifestations of Huntington's disease are increasingly recognised as being both widespread and of clinical and research significance. In premanifest and early HD, weight loss is common, may impair wellbeing and is usually treatable through simple means if detected and highlighted (Mochel, 2007). Though altered functioning of peripheral leukocytes is robustly detectable many years before predicted motor onset (Wild et al., 2008) and preliminary attempts at immune modulation in mice have shown some benefit, there is no evidence for immune

dysfunction of clinical significance in human patients. The same is true of other peripheral changes, such as testicular, bone or cardiac function, that may be detectable in premanifest and early disease.

Sleep dysfunction is widespread throughout HD and relatively prominent in prodromal and early disease. It is likely multifactorial, with contributions from anxiety, affective disorder, movement disorder, medications and disease-related impairment of the hormonal and neurological mechanisms regulating sleep (Morton et al., 2005; Arnulf et al., 2008). Thankfully, impairment of sleep is often amenable to treatment, and it has been suggested that such treatment may have benefits for other functionally important domains. Treatment options are considered below.

5. Management considerations

Chapter 15 provides a comprehensive view of clinical care in Huntington's disease, while the care of truly asymptomatic individuals was discussed above; here, we focus on an approach to patients with the very earliest symptoms and signs, in prodromal and early HD.

The broad principles that underlie management at this stage are (1) maximising remaining function and exploiting neuronal plasticity; (2) combining non-pharmacological and drug treatments; (3) forming long-term multidisciplinary therapeutic partnerships in the community and the specialist clinic; and (4) encouraging forward planning.

One striking neurobiological finding of TRACK-HD was that, despite significant striatal and white-matter atrophy in premanifest subjects more than a decade prior to predicted motor onset, significant decline was not detected in cognitive, motor, quantitative motor, oculomotor or functional measures over a 24 month period (Tabrizi et al., 2012). This implies that neuronal atrophy and / or neuronal death is already occurring in the premanifest phase of HD before symptoms or signs begin, but that plasticity - functional reorganisation of compensatory neural networks – protects against loss of function in premanifest HD (Eidelberg and Surmeier, 2011). Exploiting this plasticity, which appears to extend well into at least early HD, is perhaps the most effective means of preserving function and quality of life in HD. In practical terms, this means encouraging early access to therapies that seek to maximise function by increasing awareness of deficits and devising and practising strategies to overcome or work round them.

These findings support the notion, previously somewhat controversial, that in the cognitive / neuropsychiatric realm, non-pharmacological approaches to the management of depression, anxiety, irritability and other behavioural symptoms, such as cognitive behavioural therapy, ought to be considered alongside, or even in preference to, pharmacological treatments. Though prospective evidence for this approach is still incomplete, it is supported by small-scale studies (Silver, 2003) and expert consensus; a recommendation to consider behavioural approaches before or alongside drug treatments now features in consensus guidelines for managing the neuropsychiatric manifestations of HD (Anderson et al., 2011; Groves et al., 2011).

Equally important for behavioural manifestations of early HD is the formation of a support network spanning the community and specialist clinic. Increasingly, multidisciplinary HD clinics are complemented by the input of specialist neuropsychiatrists experienced in the care of HD patients, where therapeutic relationships are best begun at the earliest opportunity and sustained throughout the disease course; equally, the risk of acute deteriorations and constant spectre of suicide or self-harm essentially mandates the involvement of the primary care team and community psychiatric services who are best placed to offer immediate support in the event of a crisis. In our view, community psychiatry teams should be discouraged from their natural tendency to discharge HD patients from their services because subtle warning signs often precede an acute deterioration, and a combination of anxiety and apathy often discourages at-risk patients from seeking help pre-emptively. In addition to physician-led services, many HD lay organisations offer community support in the form of patient and carer groups, community specialist nurses or regional care advisers which can help patients to overcome the constraints of behavioural symptoms.

Pharmacological approaches remain, nonetheless, a mainstay for the management of neuropsychiatric and behavioural manifestations. There is little good-quality evidence for any symptomatic treatment for HD but expert opinion is relatively uniform (Mestre et al., 2009; Mestre and Ferreira, 2012). In prodromal and early HD, a low dose of a serotonin-selective reuptake inhibitor (SSRI) with anxiolytic effects, such as citalopram, can be strikingly effective for many or all aspects of the behavioural syndrome and certainly need not await formal diagnosis of motor onset. Where sleep disturbance is also a feature, mirtazepine taken at night is a useful option (Phillips et al., 2008; Novak and Tabrizi, 2010). There is a suggestion from animal studies of a possible disease-modifying benefit for SSRIs; though this has not been demonstrated in humans, it perhaps supports the use of these drugs for neuropsychiatric symptoms early in the disease (Duan et al., 2004; Peng et al., 2008).

Loss of insight remains perhaps the biggest cognitive / behavioural challenge in prodromal and early HD. It is frustrating to clinicians and relatives to witness functional deterioration in a recently well patient, but be unable to introduce helpful treatments because the patient is unaware of the symptoms. Insight in HD remains poorly studied and treatment strategies are even less well established. It is often necessary to work round the problem, instead encouraging relatives to focus on outcomes rather than instilling insight into the patient. On occasion, treatments may need to be negotiated strategically; for instance, some patients may accept a treatment for sleep dysfunction but refuse the same drug if offered for depression. Some authorities advocate the use of written contracts between carers and patients as part of a goal-directed approach, rather than one that relies on agreement about symptoms or impairments (Nance et al., 2011).

Management of motor manifestations in prodromal and early HD requires a similar approach, based on the four principles above, in terms of optimising function through exploiting plasticity. As discussed above, the most obvious motor abnormality (chorea) is generally less functionally disabling than the common but less visible impairment of voluntary motor function, for which no effective drug

treatments exist (Mestre et al., 2009). Neurophysiotherapy, implemented by expert therapists and guided by newly-available evidence-based guidelines (EHDN Physiotherapy Working Group, 2009; Quinn and Busse, 2012), is therefore the mainstay of treatment and one capable of producing palpable, sustained and functionally meaningful improvements. Again, the early establishment of a collaborative network between the community and specialist setting pays dividends; we favour initial assessment and guidance from the specialty hospital neurophysiotherapy team, with handover to the community team for ongoing therapy.

A recent expert-consensus algorithm for the management of chorea in HD (Burgunder et al., 2011) is perhaps more informative than attempts to establish guidelines based on higher-quality evidence, which has simply not been sought for many commonly-used drugs (Armstrong and Miyasaki, 2012). Where drug treatment is indicated for chorea in early disease – that is, when it is clearly functionally disabling, either physically or cosmetically – it is best to avoid neuroleptics where possible, since they can worsen voluntary function and may exacerbate involuntary movements later in the disease through tardive dyskinesia. Used sparingly, they can be a useful option in patients who also have positive behavioural symptoms such as aggression or psychosis. Tetrabenazine – the only treatment for which a good randomised-controlled evidence base exists (The Huntington Study Group, 2006; Mestre et al., 2009) - is a better first line option in early disease, though the side-effect of low mood requires great caution; mood disorder should be treated before tetrabenazine is introduced, which should be done cautiously and with vigilance about new depressive or suicidal symptoms from the patient, family members and the community team. It is not clear that neurophysiotherapy is effective for chorea *per se*, but since chorea rarely exists in isolation, a physiotherapy referral ought perhaps to be written alongside a prescription for movement disorder in most cases.

Because of its multifactorial origins (Arnulf et al., 2008), an attempt to identify the cause or causes of sleep dysfunction in early HD should be the first step in management. Poor sleep is common in prodromal and early HD and can have significant functional consequences, especially in the workplace. In many cases, treatment of underlying depression or anxiety through non-pharmacological means, and the introduction of sleep hygiene measures, will suffice. Where symptomatic drug treatment is contemplated, it should be aimed at addressing possible causes as well; hence mirtazepine in insomniac patients with low mood or anxiety, or low-dose risperidone at night for patients whose sleep is disturbed by chorea. Mounting evidence for a possible role of deranged melatonin production in HD in association with sleep dysfunction (Morton et al., 2005; Aziz et al., 2009), a suggestion from animal models that restoration of sleep-wake cycles may improve cognition (Pallier and Morton, 2009) and studies indicating that melatonin may be neuroprotective (Wang et al., 2011) argue for a possible role for melatonin supplementation in premanifest and early disease for patients with disordered sleep. Some authorities advocate hypnotic or melatonin treatment at night combined with stimulant (modafinil) treatment in the morning to impose a strict sleep-wake cycle (Phillips et al., 2008). Randomised clinical trials in this area are sorely needed.

It is worth giving special attention to employment and driving in early HD. These are two functional domains, often central to patients' well-being and sense of self-worth, that become impaired and must be given up during this stage, often in the face of extreme reluctance and poor insight.

Legal protections in employment law vary between nations, but most offer some formal protections for disabled people. In the UK, for example, it is illegal for employers to dismiss or treat an employee negatively because of a disability. On occasion, it may be necessary to remind employers that they have legal liabilities in this regard or suggest that the patient consider legal avenues if an employer is being unreasonable. We strongly recommend that patients with Huntington's disease who feel that their ability to work may be deteriorating inform their employers about their diagnosis, to ensure that their job is legally protected. Once diagnosis is revealed, regular assessment should take place according to occupational risk, and the HD clinical team may offer support and education to employers about Huntington's disease, the problems it can cause, and the adaptations and accommodations that may be necessary to enable the patient to continue working (Novak and Tabrizi, 2010).

Deciding whether to reveal a 50% risk of HD, or a positive predictive test result, to an employer is equally difficult, and again employment law differs between nations. In the USA, the Genetic Information Nondiscrimination Act (GINA) prohibits discrimination on the basis of genetic information in employment and health insurance provision. In contrast, the UK offers no legal protection to those at risk of HD. In general, premanifest gene carriers are not obliged to disclose a positive predictive test result to their employer, but must do so if asked to do so specifically, e.g. in a health questionnaire. Some employers such as the police or military may place restrictions, based on family history, on at-risk people or asymptomatic expansion carriers. In a Canadian survey of 233 tested and untested people at risk of Huntington's disease, 6.9% reported genetic discrimination related to employment (Bombard et al., 2009).

Because of cognitive and behavioural symptoms during prodromal HD, driving can be impaired well before official motor onset. After onset, impairment is usually multifactorial and progressive, though many patients remain able to drive safely for several years (Rebok et al., 1995). Again, the legal requirements placed upon patients and medical professionals differ between countries, but in general, because of the risk to the individual concerned and other road users, it is essential to err on the side of safety. In most territories there is no requirement to inform the licensing authorities of a positive predictive test, but patients should do so at the first suggestion of symptoms or signs. Usually the role of the clinician is in advising the patient to contact the licensing authorities and providing factual reports about physical, cognitive and psychiatric impairment. Occasionally, in patients with marked loss of insight, it is necessary (and indeed mandatory) for a clinician to report impairment directly to the authorities. For many patients with borderline functioning that may be highly context-specific, it is not practical for the community or outpatient team to comment definitively on driving safety, and reassessment through a practical driving test is the best option (Rebok et al., 1995; Beglinger et al., 2012).

Specialist speech and language therapists, experienced in managing HD and guided by evidence-based guidelines (Hamilton et al., 2012a; Hamilton et al., 2012b) are best placed to distinguish between behavioural and mechanical dysphagia. Guidelines are now also available for dietetic input in early HD (Brotherton et al., 2012); in our experience, it frequently falls to the HD specialist team to educate patients, families and primary care teams about the need for dietary assessment and supplementation. Occupational therapists are well placed to take an overview of the patient's level of function at home and at work, and are too frequently overlooked in prodromal and early HD where the opportunity to preserve function is greatest (Cook et al., 2012).

6. Detecting the earliest disease changes and understanding the natural history of premanifest and early HD

In addition to helping to establish a clearer notion of prodromal HD, longitudinal studies of human volunteers, have improved our understanding of the neurobiology of HD, and in particular the earliest disease-related changes that can be detected using novel techniques. Though it is premature for this new knowledge to permeate the clinical care of patients, they are helping to shed light on the longstanding debate about when HD begins and to what extent it is a disease of development, dysfunction or degeneration.

One widely-supported integrated model (Figure 3) acknowledges a role of mutant huntingtin in development, based on animal studies (Molero et al., 2009) and tentatively supported by preliminary human studies (Nopoulos et al., 2011; Lee et al., 2012). However, a developmental role appears minor, reversible and of doubtful clinical significance. The earliest detected change in accessible human tissue, aside from mutant huntingtin in leukocytes (Weiss et al., 2012), is mild elevation of IL-6 in peripheral plasma, thought to be due to an effect of mutant huntingtin within myeloid cells; this was found in subjects estimated to be 16 years before onset and may well be a lifelong phenomenon (Wild et al., 2008). To all intents and purposes, though, it seems that expansion-carriers leave adolescence on a level playing field in terms of brain structure and function.

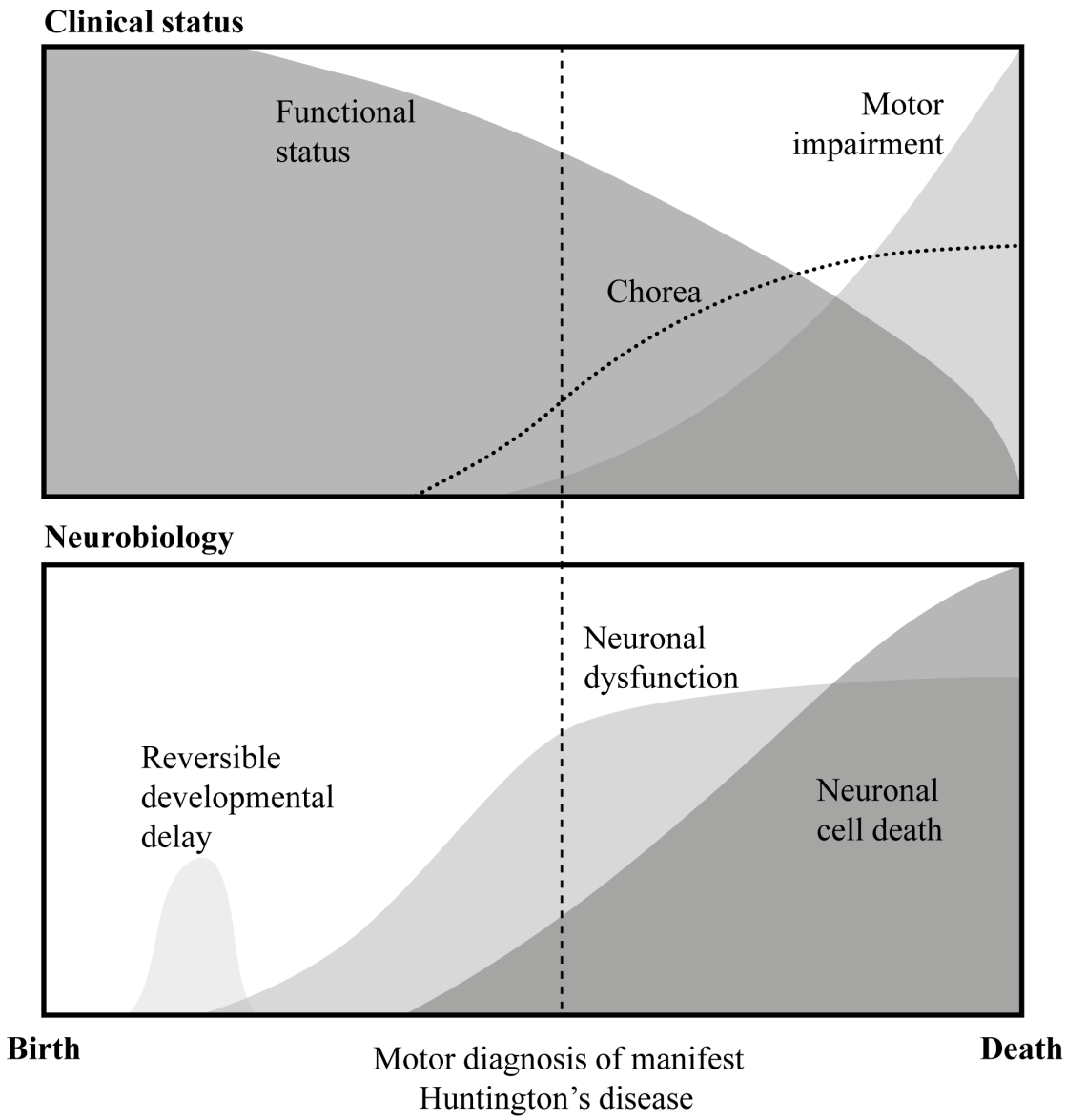

Figure 3 A model for the neurobiological basis of clinical symptomatology in Huntington's disease. Subtle signs and symptoms of Huntington's disease begin years before a motor diagnosis can be made, and correlate with neurobiological changes such as striatal atrophy, giving rise to the disease prodrome. Early in the disease course, neuronal dysfunction is likely to be important, but later, neuronal cell death in vulnerable regions of the brain is predominant and correlates with motor impairment and functional disability. Adapted from (Ross and Tabrizi, 2011) with permission of Elsevier.

Overall, though, the first clinically significant disease process is neuronal dysfunction. Direct evidence for synaptic dysfunction is plentiful in animal models (Cummings et al., 2006) and evidence that dysfunction is reversible now comes from both conditional knockout models (Yamamoto et al., 2000) and, more recently, nucleotide-based gene silencing in mice (Harper et al., 2005; Carroll et al., 2011).

Reversal of dysfunction appears possible even to the extent that reversal of both neuropathological and neurological abnormalities occur when mutant huntingtin production is reduced.

Demonstrating that neuronal dysfunction exists in humans remains challenging. It has been hinted at by functional MRI studies (Paulsen et al., 2004; Novak et al., 2012). It is unclear whether fMRI results of regional over- and under-activation in premanifest HD can be interpreted as signs of dysfunction, highlight compensatory overactivity, or, perhaps most likely, are indicative of both.. In a sense, this is evidence for a role for neuronal plasticity in premanifest HD – effectively the corollary of neuronal dysfunction. TRACK-HD has now provided compelling evidence that structural volume loss – widely accepted as evidence for neuronal loss (Fox et al., 1996) and seen robustly in subjects many years before expected onset of manifest disease – is not associated with deterioration in even the most sensitive tests of function, included detailed cognitive, quantitative motor and oculomotor assessment over a 24-month time interval (Tabrizi et al., 2012). This implies that, during a phase when we know structural pathology has begun, and assume that neuronal dysfunction is also afoot, neuronal or synaptic plasticity furnishes the brain with compensatory networks that allow functional normality or near-normality to be maintained.

These compensatory mechanisms are now the subject of intense research interest since enhancing or preserving them may afford opportunities for extending high-quality life. Synaptic function, in particular, is a focus for therapeutic development, with agents including memantine (Milnerwood et al., 2010) and phosphodiesterase modulation (Giampà et al., 2010) being examined as possible enhancers of function, or reversers of dysfunction, in HD. In parallel, concerted efforts are underway (e.g. the multinational TrackOn-HD study) to study the compensatory neural networks in premanifest human HD expansion carriers. An ongoing complementary initiative, FuRST-pHD, aims to develop a novel cognitive rating scale to expose and quantify the subtle cognitive changes of prodromal HD (Vaccarino et al., 2011).

In terms of detecting neurodegeneration, structural MRI has emerged from the large prospective cohort studies as the most robust biomarker of neuronal atrophy and / or loss in HD. TRACK-HD identified within-subject caudate and white-matter atrophy rates as the most robust correlates of motor onset. In the same cohort, automated quantitative motor measurement of subclinical chorea, grip force and speeded tapping were also significantly elevated in those who progressed to manifest HD, suggesting a possible role for these methodologies in uncovering the earliest motor abnormalities in HD (Tabrizi et al., 2012). The 3-year followup data from TRACK-HD identified several measures that can reliably predict progression in premanifest HD expansion carriers – independently of CAG repeat length – including timed tapping and grey-matter volume, raising the prospect of 3-year clinical trials of experimental therapeutics aiming to prevent symptom onset (Tabrizi et al., 2013).

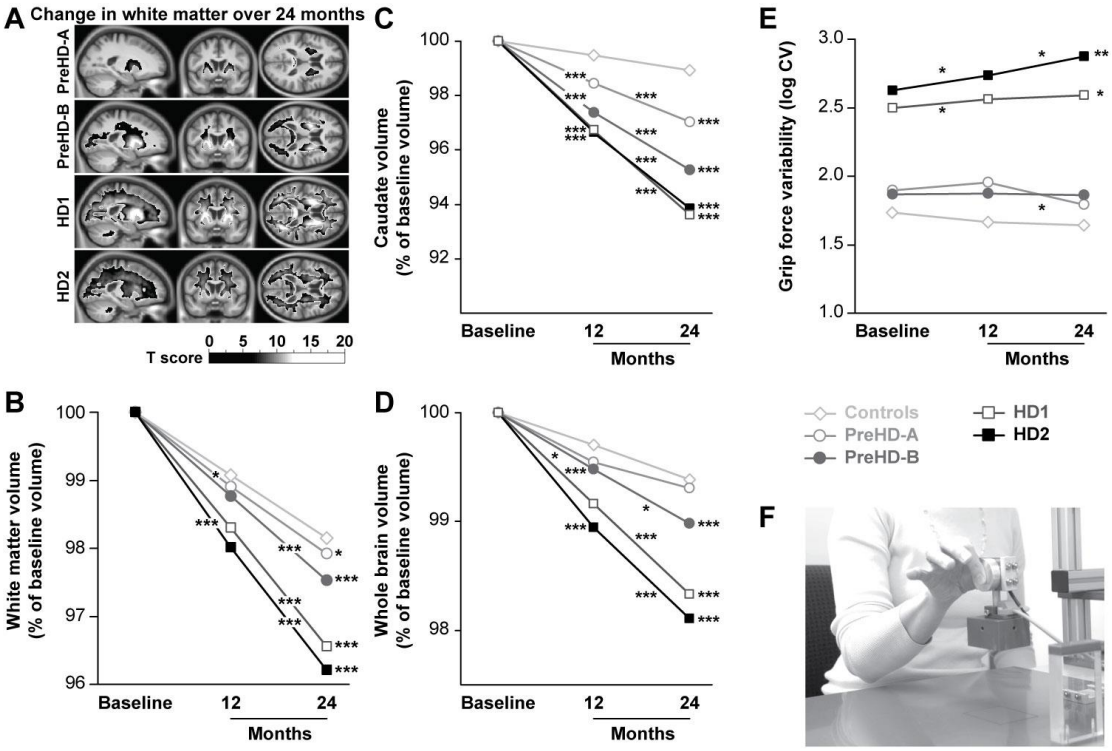

Figure 4 Example of the most robust changes in premanifest and early HD identified by the TRACK-HD study. Change in white-matter volume over 24 months, seen as statistical parametric maps and (B) presented as atrophy rates by group. (C) Caudate atrophy rates. (D-E) Grip force variability assessed using computerised quantitative motor assessment. Adapted from (Tabrizi et al., 2012) by permission of Elsevier.

What is the potential utility of our increasing ability to detect the earliest changes in the brains of HD genetic expansion carriers? First it is important to restate that, at present, none has been sufficiently validated or accredited to be considered suitable for conveying useful clinical information in individual cases. Their important role currently is on a research basis as it gives insights into the neurobiology and time-frame of the neurodegenerative disease process in HD which is critical to understanding the disease as a whole in humans, and to developing and evaluating potential disease-modifying therapies The immediate application of our improved ability to detect previously covert abnormalities in HD will be for the conduct of clinical trials of agents aimed at ameliorating the degenerative process. TRACK-HD has provided an evidence-based battery of tests as proposed outcome measures in early HD, and ongoing analyses seek to define similar potential outcome measures for clinical trials in prodromal and premanifest HD. As we shall see in Chapter 17, many such trials are expected in the next decade and evidence-based objective measures, alongside traditional clinical endpoints, will hopefully enable firmer conclusions to be drawn from them.

Robust predictors of motor onset or disease progression, including brain atrophy measurements and other measures yet to be unearthed in early premanifest disease, may provide a means for any drug

successful in early disease to be tested in premanifest cohorts, or may provide additional stratification criteria for clinical trials. Ultimately, we hope to develop not only disease-slowing therapies but also a full understanding of how those therapies interact with very early measures of disease processes, to enable the ultimate goal of preventing deterioration and prolonging the period where expansion-carriers are truly asymptomatic and functioning at their best.

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