Beyond the brain: widespread pathology in Huntington’s disease

Jorien MM van der Burg, Maria Björkqvist, Patrik Brundin

Huntington’s disease (HD) is an inherited neurodegenerative disorder caused by a polyglutamine stretch in the huntingtin protein. Today, more than 15 years after the genetic defect underlying HD was discovered, the pathogenesis is still not well understood and there is no adequate treatment. Research into this disorder has conventionally focused on neurological symptoms and brain pathology, particularly neurodegeneration in the basal ganglia and cerebral cortex. Mutant huntingtin is, however, ubiquitously expressed throughout the body. Indeed, contrary to earlier thinking, HD is associated with abnormalities in peripheral tissues. These abnormal changes are not all secondary to brain dysfunction, but most seem to be directly caused by expression of mutant huntingtin in peripheral tissues. In this article, we highlight this emerging field of research and how it might affect our understanding of the pathogenesis of this disease, the development of novel biomarkers of disease progression, and the identification of new potential treatments.

Introduction
Huntington’s disease (HD) research has conventionally focused on the brain for obvious reasons: HD’s core symptoms include motor abnormalities such as hyperkinesia and hypokinesia, as well as psychiatric and cognitive problems (the panel provides an overview of HD). These symptoms have all been linked to neurodegeneration in the basal ganglia and cerebral cortex.

In addition to the classic symptoms, HD is complicated by other features, such as weight loss and skeletal-muscle wasting, which are not necessarily directly associated with changes in brain functions (figure 1). These features sometimes appear early in the disease course and can eventually contribute substantially to both morbidity and mortality. These symptoms have been suggested to be secondary to general sickness or to be the consequences of neurological dysfunction. However, a growing body of evidence indicates that these changes might be due to the direct effect of mutant huntingtin (the toxic protein that causes HD) on peripheral tissues. This thinking is largely derived from recent studies in animal models of HD, but the fact that similar abnormalities also occur in peripheral tissues of patients is gradually becoming evident. In this article, we propose that an improved understanding of changes in peripheral tissues in HD could give insight into the pathogenesis of the disease, lead to discovery of novel biomarkers of disease progression, and could open new avenues for treatment.

HD is not only a brain disorder
Several facts indicate that peripheral features of HD, such as weight loss and skeletal-muscle wasting, might have little or nothing to do with neurological dysfunction or general sickness. First, huntingtin is expressed in many tissues and organs in human beings and other mammals. The precise function of huntingtin is unclear, but this protein seems to be involved in several cellular processes, including transcriptional events, protein trafficking, and vesicle transport. Studies in knock-out mice have revealed that absence of huntingtin leads to defects in all three germ layers and is embryonically lethal, indicating that huntingtin is essential for many tissues. Indeed, knocking down huntingtin expression in zebrafish results in peripheral defects, such as impaired haemoglobin production. Second, mutant huntingtin seems to affect organelles and functional systems that are essential to all cells (eg, mitochondria, the ubiquitin–proteasome system, caspases, and chaperones). As a result, cells from peripheral tissues from patients with HD and from animal models have, for example, mitochondrial dysfunction and transcriptional defects. Moreover, intracellular huntingtin aggregates—the hallmark of HD neuropathology—are present in peripheral organs of transgenic mice with HD. Third, dysfunction of peripheral cells also occurs when these cells are isolated and is not secondary to brain dysfunction. For example, monocytes isolated from HD gene carriers, which express mutant huntingtin, are pathologically hyperactive in response to stimulation from lipopolysaccharide. Fourth, when mutant huntingtin is expressed only in cardiomyocytes of wild-type mice, the animals develop heart failure.

The above observations all support the hypothesis that peripheral abnormalities in HD could be caused directly by local expression of mutant huntingtin and could occur independently from neurological defects or general malaise.

Non-neuronal abnormalities might contribute to symptoms
In this section we discuss in more detail how abnormalities in peripheral tissues could underlie various signs and symptoms of HD. Patients with this disorder have several non-neurological features, including weight loss and skeletal-muscle wasting. Although less
Panel: Overview of Huntington’s disease*

First accurate description
In 1872 by George Huntington

Genetic disorder
Autosomal dominant neurodegenerative disorder

Epidemiology
4–8 per 100 000

Onset
First symptoms can start at any age, but mean age at onset is between 35 and 45 years

Clinical presentation
Classic neurological symptoms
• Motor symptoms
• Cognitive deterioration
• Psychiatric and behavioural problems

Other clinical presentation features
• Weight loss
• Atrophy of skeletal muscle
• Sleep disturbance
• Autonomic disturbances

Cause
A mutation in HTT causes the formation of the mutant protein huntingtin. Normal individuals have less than 36 CAG repeats in HTT. Individuals with >39 CAG repeats will develop Huntington’s disease. Reduced penetrance occurs with 36–39 CAG repeats.

Pathogenesis
The role of normal huntingtin is not completely clear, but when mutated it causes, for example, the formation of intracellular inclusion bodies, impaired intracellular transport, defected gene transcription, and apoptosis.

Genetic animal models
Some of the most widely studied mouse models
• R6/2: expresses exon 1 of human mutant HTT with about 150 CAG repeats
• YAC 72: expresses full-length human mutant HTT with 72 CAG repeats, created using a yeast artificial chromosome as vector
• YAC 128: expresses full-length human mutant HTT with 128 CAG repeats, created using a yeast artificial chromosome as vector
• N171–82Q: expresses the 171 amino acids at the N-terminal of mutant huntingtin with 82 CAG repeats
• HdhQ92: model with 92 CAG repeats knocked in into the mouse Htt

Other genetic animal models
• Caenorhabditis elegans models
• Drosophila melanogaster models
• Transgenic rhesus macaques

* A comprehensive overview of HD is provided by Walker and colleagues.

Huntington’s disease. Reduced penetrance occurs with 36–39 CAG repeats.

Transgenic rhesus macaques
• Drosophila melanogaster
• Caenorhabditis elegans

Other genetic animal models
• HdhQ92: model with 92 CAG repeats knocked in into the mouse Htt
• YAC 128: expresses full-length human mutant HTT with 128 CAG repeats, created using a yeast artificial chromosome as vector
• R6/2: expresses exon 1 of human mutant HTT with about 150 CAG repeats
• YAC 72: expresses full-length human mutant HTT with 72 CAG repeats, created using a yeast artificial chromosome as vector
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thoroughly investigated, glucose intolerance, osteoporosis, cardiac failure, gastrointestinal abnormalities, and testicular atrophy might also belong to the HD phenotype in affected patients (figure 1). These features of the disease are clinically important as they reduce quality of life and, in some cases, correlate with disease progression and contribute to early death.

Weight loss
One of the most common peripheral abnormalities that affects nearly all individuals with HD, and which is not necessarily associated with pathology of the nervous system, is unintended weight loss. This weight loss is progressive, beginning as minor loss in presymptomatic gene carriers and ending with profound cachexia in advanced-stage patients,30–38 and correlates with CAG repeat number.39 Why patients with HD lose weight is not known. Many studies have indicated that this feature is not secondary to hyperactivity30,34,35 or anorexia,30,35,38,40 but results from an increased metabolic rate.38,40,42 Patients with HD have a higher body mass index at onset of symptoms tend to have a slower rate of disease progression,41 suggesting that weight loss could be a valuable target for therapeutic intervention.

According to numerous studies, most of which in transgenic mouse models, several tissues and organs that are important in weight regulation might be affected in HD (figures 2 and 3). For example, the digestive system, which is important for nutrient absorption, is dysfunctional. Patients suffer from xerostomia,43 which could affect taste, mastication, and swallowing, all of which might contribute to weight loss. In the R6/2 mouse, the most widely studied transgenic animal model of HD, the number of ghrelin-producing neurons is reduced in the stomach.44 Ghrelin normally stimulates food intake and inhibits energy expenditure; therefore, a loss of this hormone might contribute to weight loss. The pancreas is also affected and both patients with HD and mice models of the disease tend to develop impaired glucose tolerance.45–48 In a recent study by Lalic and colleagues,42 an impairment in insulin-secretion capacity alongside a decrease in insulin sensitivity was seen in patients with HD compared with control individuals. In mice, pancreatic islet cells are atrophic and exhibit intranuclear inclusions,39,51 resulting in defects in insulin, somatostatin, and glucagon production.45 In patients, although islets are of normal size, transcriptional dysregulation in islet cells might underlie the increased tendency to develop impaired glucose tolerance.51 One study indicated that mutant huntingtin might also affect the liver. Transcription of urea-cycle enzymes is impaired in the liver of mice with HD, leading to high circulating concentrations of ammonia with concomitant brain damage and locomotor dysfunction.52 A low protein diet reduced ammonia concentrations in the plasma, and ameliorated brain damage and locomotor function in these mice.56
In addition to the digestive system, adipocytes might be affected in HD. Endocrine signals from white adipose tissue, which normally reflect energy levels within the body, are affected in two HD mouse models. Expression of fat-storage genes and concentrations of the adipokine hormones leptin and adiponectin are impaired in these mice, which might contribute to weight loss. These transcriptional defects are a direct consequence of mutant huntingtin expression in the mouse adipocytes and can be replicated in an adipocyte cell line.

Skeletal-muscle atrophy

Skeletal-muscle wasting is another hallmark of HD. The mechanisms underlying muscular atrophy in this disorder are unclear and, of note, the skeletal muscles undergo substantial wasting, despite the muscles being highly active as a result of hyperkinesia. The muscle wasting is possibly due to defects caused by the presence of mutated protein in myocytes. Mutant huntingtin forms inclusion bodies in muscle cells of R6/2 mice and disrupts gene expression similarly to its effect in the brain. This finding suggests that similar pathogenetic mechanisms are operative in neurons and muscle cells. Apart from affecting transcriptional regulation, mutant huntingtin is known to affect mitochondrial function. Studies on cultures of skeletal-muscle cells from patients with HD revealed several mitochondrial abnormalities, including respiratory-chain dysfunction, morphologically abnormal cristae, cytochrome c release, and apoptosis. In vivo studies also revealed altered muscle energy metabolism in this disorder.

Hence, myocytes are affected in HD, possibly as a direct effect of mutant huntingtin, and muscles undergo atrophy as a result. This finding opens up new possible treatment strategies and novel ways of monitoring disease progression.

Cardiac failure

Cardiac failure occurs in about 30% of patients with HD (compared with only 2% in age-matched controls) and is a leading cause of death in these patients. Nothing is known about the pathophysiological mechanism underlying cardiac failure in this disorder, but failure of the autonomic nervous system might play a part. Alternatively, cardiac failure might be caused by the effects of mutant huntingtin in cardiomyocytes. In R6/2 mice, the myocardium is atrophic, mitochondria in cardiomyocytes have abnormal shapes, and cardiac output is reduced by 50%. Cardiomyocyte-specific expression of polyglutamine fragments with 83 CAG repeats in wild-type mice induces aggregate formation, autophagy, and necrotic death of cardiomyocytes, eventually leading to heart failure. Taken together, these experimental data indicate that heart failure in HD could be a direct consequence of mutant huntingtin expression in cardiomyocytes, and clinical studies on cardiac tissue of patients are needed to resolve this matter.

Testicular atrophy

The highest levels of huntingtin expression are found in the brain and testes. Although fertility is unaffected in patients with HD, men have reduced testosterone concentrations as well as testicular pathology with reduced numbers of germ cells and abnormal seminiferous tubule morphology. Reduced plasma concentrations of testosterone correlate with worsening of the disease. Similarly, both the R6/2 and YAC128 mouse models of HD have testicular atrophy, albeit to a greater extent than patients. In R6/2 mice, concentrations of gonadotropin-releasing hormone are reduced, which suggests that the effects might be secondary to hypothalamic dysfunction. In YAC128 mice, however, testicular degeneration develops before any evidence of decreased testosterone concentrations or loss of gonadotropin-releasing hormone neurons in the hypothalamus, suggesting that testicular pathology results from a direct toxic effect of mutant huntingtin in the testes.

Osteoporosis

Data from two preliminary reports suggest that osteoporosis might also be part of the HD phenotype and that its severity correlates with the number of CAG
repeats. The reason for decreased bone mineral density in this disorder is not known; it might be secondary to neuroleptic treatment, might result from immobility, but could also be a direct effect of the disorder itself. For example, decreased bone mineral density can result from disrupted endocrine signalling, such as increased cortisol concentrations. R6/2 mice have decreased bone density, along with increased concentrations of cortisol, wasting of skeletal muscle, accumulation of abdominal fat, and insulin resistance, similar to a Cushing-like syndrome. These findings led to the observation of increased urinary concentrations of cortisol in patients with HD. Recent studies have confirmed that there are increased cortisol concentrations in these patients, but alterations are probably too small to cause a Cushing-like syndrome.8 These findings led to the observation of increased urinary concentrations of cortisol in patients with HD.9,10,12,13 Additionally, adenosine A2A receptor function and monoamine oxidase activity are disrupted. Blood plasma samples of patients with HD show signs of immune activation, such as increased concentrations of interleukins 8 and 6.14,15 Altered inflammatory signalling might contribute to several features of HD, including weight loss and muscle wasting. Prolonged inflammatory cytokines are associated with muscle atrophy, exerted through inhibition of myogenic differentiation and enhanced apoptosis.16,17 Moreover, these cytokines can affect energy metabolism and body weight.18 The immune system in HD might be activated in reaction to cellular pathology, such as aggregate formation, oxidative damage or necrotic cell death.
However, concentrations of IL-6 are already increased as early as 16 years before the predicted onset of symptoms. Moreover, as mentioned earlier, isolated monocytes from patients with HD and asymptomatic mutant HTT gene carriers express mutant huntingtin and are pathologically hyperactive in response to stimulation. These observations all suggest that inflammatory changes in this disease result from dysfunction of immune cells and are not secondary to brain pathology or general sickness.

Are changes in peripheral tissue secondary to brain dysfunction?

There are many peripheral abnormalities in HD that seem to occur independently from neuronal dysfunction. However, brain pathology, for example in the hypothalamus, could lead to altered endocrine signalling and secondary changes in peripheral tissues. Several neurodegenerative disorders, including Alzheimer’s disease, can also be complicated by peripheral abnormalities, such as weight loss, which could suggest a role of the brain in causing these features. The hypothalamus is affected in patients with HD and in transgenic mice, and its pivotal role in endocrine regulation means that the pathology restricted to this brain structure can affect the whole body. Changes have been found in several of the hypothalamic–pituitary axes and include altered concentrations of luteinising hormone, growth hormone, and cortisol. Peptides that could possibly be linked to caloric intake and weight loss are also affected in this disorder. In the hypothalamus of HD mice, the expression of vasopressin, oxytocin, cocaine, and amphetamine-regulated transcript peptide (CART), gonadotropin-releasing hormone, and vasoactive intestinal polypeptide and its receptor are reduced. Despite multiple changes in the hypothalamic or pituitary control of endocrine functions, results from various studies indicate that brain dysfunction might not be involved in the genesis of many peripheral abnormalities in HD. Decreased concentrations of testosterone in patients with HD do not correlate with decreased concentrations of luteinising hormone. On the contrary, patients with lowest testosterone concentrations have normal concentrations of luteinising hormone.

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**Figure 3:** Peripheral pathology in animal models of Huntington’s disease

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<th>Skeletal muscle</th>
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<td>Morphological changes</td>
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suggesting that altered testosterone production is not caused by defects in hypothalamic–pituitary signalling. Mice with HD can also exhibit testicular pathology without evidence of disrupted hypothalamic–pituitary signalling.67 Additionally, changes in hypothalamic peptides regulating energy metabolism and body weight were not clearly linked to weight loss in HD mice;46 neither did decreased vasopressin concentrations lead to increased water consumption in these mice.46 A study in functioning of the hypothalamic–pituitary axes in patients with HD was also unable to link several observed peripheral abnormalities to disrupted neuroendocrine signalling.71 Finally, some peripheral alterations are detectable many years before neurological symptoms are evident and neuronal pathology is evident and neurological symptoms are present,74 suggesting that the central and peripheral changes are not linked.

Taken together, these findings suggest that peripheral abnormalities do not necessarily arise from altered hypothalamic–pituitary signalling, but are due to primary defects in peripheral organs. Contrary to previous thinking, peripheral defects might even contribute to brain pathology.64,65 Therefore, HD can be viewed as a systemic disorder, in which many organs and tissues are affected and changes in one organ trigger malfunction in another. To unravel the precise role of each of these organs and tissues in this disease, animal models that selectively express mutant huntingtin in certain organs or brain regions, such as the mouse model with cardiomycocyte-specific expression of mutant huntingtin,95 might be helpful.

Understanding HD by looking into peripheral tissues

Having described the many peripheral abnormalities and their possible origins, we now discuss how discoveries of these defects might help to resolve outstanding problems in HD. Investigations of peripheral abnormalities could lead to better understanding of the pathogenesis, development of novel therapies, and the discovery of biomarkers of disease progression. Peripheral tissues are typically easier to study than the CNS. Sampling of peripheral tissues (eg, blood cells) can be minimally invasive and inexpensive compared with techniques to study brain function, such as advanced brain imaging. Furthermore, peripheral cells can be isolated from living patients, enabling the study of pathological mechanisms in cells affected by HD throughout the disease course.

Cellular mechanisms underlying peripheral pathology

Studies in peripheral tissues now substantially contribute to our understanding of HD pathogenesis.6,62,17,20,26,46,54,66 Changes in peripheral cells, such as mitochondrial dysfunction,6,17,11 cholesterol defects,6,77 and transcriptional alterations,6,11,12 often resemble abnormalities in the brain and provide valuable insight for disease mechanisms. For example, a recent study in lymphocytes from patients with HD detected altered transcription of neuronal RE1/NRSE (repressor element-1/neuron restrictive silencer element), which had only been described in post-mortem HD brains, but also occurs in vivo.92 Conversely, studies in peripheral tissues have led to findings that have resulted in the realisation of similar changes in brain tissue.

Transcriptional and mitochondrial defects are important pathogenetic mechanisms. These defects are involved in both peripheral and CNS pathology in this disease and could explain many symptoms. A transcriptional defect that could be accountable for several clinical features of HD is the altered expression of PPARγ coactivator 1α (PGC-1α). PGC-1α regulates mitochondrial biogenesis and respiration, and is downregulated in several tissues of patients with HD, including brain, muscle, and fat tissue.60,31,32 In the brain of knock-in HD mice (with 140 CAG repeats inserted into the murine huntingtin gene), expression of PGC-1α is reduced in medium-sized spiny neurons, but increased in cholinergic interneurons.31 Therefore, changes in PGC-1α might be linked to the selective vulnerability of medium-sized spiny neurons that is characteristic of this disease. Decreased expression of PGC-1α might underlie several other HD-associated changes. For example, this change might be linked to cardiomyopathy in HD mice,44 as the myocardium largely depends on mitochondrial energy and expresses high concentrations of PGC-1α. Other organs that highly depend on ATP, such as the kidneys, might also be affected in HD. However, to our knowledge, a study into this possibility has not been done.

Taken together, peripheral abnormalities often resemble brain pathology, and certain pathogenic mechanisms, such as transcriptional dysregulation and mitochondrial dysfunction, could underlie many symptoms of HD.

Novel targets for therapeutic interventions

The study of peripheral abnormalities in HD has resulted in the discovery of novel potential therapeutic targets. The treatment of liver and pancreas defects ameliorated brain pathology and neurological symptoms in mice with HD.60,67 Furthermore, treatment of non-neurological symptoms could improve quality of life and postpone premature death. A starting point for a novel therapy might be the observation that a higher body mass index is associated with a slower progression of disease.43 A possible cause-and-effect association between increased body weight and slower progression of neurological symptoms in HD is not yet clear. It would be interesting to examine whether taking measures to increase body mass index slows down the progression of neurological symptoms. Trejo and co-workers46 showed that a higher caloric intake stabilises body weight in patients with HD, but they did not specifically address whether disease progression was affected. With regard to possible effects
of treating impaired glucose tolerance in HD, animal studies have provided some information. Chronic treatment with glibenclamide, a hypoglycaemic drug that induces release of insulin, does not improve the disease or the lifespan in R6/2 mice.39 By contrast, metformin does increase lifespan and reduces motor symptoms such as hind-limb clasping in male R6/2 mice.39 31 The antidiabetic glucagon-like peptide 1 receptor agonist exendin-4 also exerts beneficial effects in R6/2 mice; this drug suppresses pathology in the pancreas and the brain, leading to improved motor function and survival.31 However, the precise mechanism of action of exendin-4 in these experiments is not clear. This drug also exerts anti-inflammatory effects and promotes brain plasticity, which could support functional recovery.39

Strategies to counteract cardiac failure in HD could possibly both improve quality of life and prevent early death. In future studies targeting cardiomyopathy in this neurodegenerative disease, non-invasive ultrasonography could provide immediate and objective feedback with regard to possible treatment effects. Treatment of other peripheral abnormalities, including testicular degeneration has, to our knowledge, never been attempted. Decreased concentrations of testosterone are generally associated with decreased libido, osteoporosis, and wasting of skeletal muscle. These signs and symptoms have all been detected in either patients or mice with HD.35,37 Reduced testosterone concentrations in the blood correlate with disease severity, as measured by motor and functional scores.37 Moreover, low concentrations of testosterone have been associated with neuronal loss,105 which could possibly contribute to HD neurodegeneration. Patients might therefore benefit from hormonal replacement therapy.

**Discovery of new biomarkers**

Biomarkers to monitor or predict disease progression in HD are needed to assess therapeutic responses during clinical trials. Assessment of symptoms is typically not sufficiently sensitive, because of the protracted course of the disease, and the paucity of rigorous objective tools to assess clinical changes means that there is a risk for observer bias. Moreover, there are no methods to assess disease-associated changes in gene carriers who do not have overt symptoms.42 Unlike most other neurodegenerative diseases, every patient with HD carries the mutation and everyone with the mutation will develop the disease. HD therefore offers unique possibilities to detect early changes of disease course. Direct measures of peripherally manifested symptoms, such as xerostomia10 and weight loss,39 could possibly translate into potential biomarkers. Changes in muscle gene expression, which are altered during the course of the disorder, could also be used to track disease progression.39,39 Data from several studies have suggested that peripheral alterations that manifest in the blood or plasma could be potential biomarkers of HD progression. Changes in nutritional and metabolic markers,26,84 as well as markers of endocrine dysfunction,7,30,109 have been suggested. Plasma 24S-hydroxycholesterol is a promising biomarker that reflects the early progression of neurodegeneration in HD.108 Proteins of the immune system (eg, clusterin and interleukin 6) also indicate disease progression.28,84 Altered function of peripheral blood cells has also been suggested as a biomarker. For example, adenosine receptor A2A function in peripheral blood is altered in HD10 and blood-borne immune cells from patients with HD are hyperactive in response to stimulation from lipopolysaccharide.28 The idea that the effects of mutant huntingtin in peripheral cells (eg, blood cells) can be used to monitor disease progression is appealing. One major criticism of plasma markers of neurodegenerative diseases is that they might be non-specific, or that they could be epiphenomena caused by a general illness state. Certainly, in advanced HD, nutritional, metabolic, and infective pathology are likely to confound any findings. However, changes that are seen even before the onset of overt motor symptoms will be of interest.

**Conclusions and future directions**

Peripheral abnormalities are important features of HD. Most of these changes have been described in animal models of HD, but it is gradually becoming evident that similar abnormalities occur in peripheral tissues of patients. Such defects might result directly from mutant huntingtin expression in peripheral tissues and might be involved in HD symptoms. Recent studies on peripheral pathology in HD have provided important insights into underlying disease mechanisms. In the future, these studies might pave the way for new therapies and new markers to monitor disease progression. Finally, treatment of peripheral symptoms in HD could prove important, and positively affect quality of life and prevent early death.
Contributors
JMMvdB initiated the project, drafted the first version of the Review, and composed the panel and figures. MB and PB contributed with additional sections and, together with JMMvdB, edited later editions of the paper. All authors agreed on the final version of the review.

Conflicts of interest
We have no conflicts of interest.

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