Section I General principles

Chapter 1

Phenomenology, classification, and diagnostic approach to patients with movement disorders

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Introduction

In this introductory chapter, we will discuss the phenomenology of movement disorders and its importance in classification and diagnostic work-up in patients presenting with one or more types of movement disorders. We will place great emphasis on the most important step in this diagnostic process, which is the clinical approach based on recognition of the phenomenologic characteristics of the movement disorder. An accurate clinical description and adequate recognition of the type of movement disorder (or multiple types, as is often the case) in turn forms the basis for a tailored set of ancillary investigations to confirm the clinical suspicion. Thanks to rapid technological advancements (for example, in the fields of genetics and functional imaging), clinicians now have a battery of advanced ancillary investigations at their disposal. In this chapter, we will discuss the rational use of some of the most commonly required tests. However, we should point out that the clinical pattern recognition remains the vital starting point for any diagnostic approach, and that many ancillary investigations offer relatively little added value over and above the diagnostic accuracy of a clinical neurological examination (Constantinescu *et al.* 2009; Seppi and Schocke 2005; Morris and Jankovic 2012).

Here, we propose a step-wise approach that can be used for the evaluation of patients with a movement disorder. The algorithm, depicted in Figure 1.1, illustrates this diagnostic process (Abdo *et al.* 2010). The *first step* is the recognition of the dominant type of movement disorder that is present in any given patient. The *second step* is to extract all relevant other neurologic or non-neurological features, both from the history and the neurological examination. These first two steps lead to a clinically based syndrome, with associated corresponding differential diagnosis. The *third step* should consist of a limited set of ancillary tests to further narrow down the differential diagnosis, and to hopefully prove the diagnosis. Our main purpose here is to illustrate this generic diagnostic approach, and to give some examples of how this would work in clinical practice. It is not our goal to elaborate on the complete differential diagnosis of the various types of movement disorders, nor to discuss the clinical characteristics of the many neurodegenerative disorders that can include one or more movement disorders as part of their clinical presentation. This is discussed in more detail in other chapters of this book. Elements of the diagnostic approach illustrated here have been published elsewhere (Abdo *et al.* 2010; Aerts *et al.* 2012). Many of the movement disorders described below are illustrated by videos (Videos 1.1 to 1.23).

The first step: recognition of the dominant type of movement disorder

The first step is to identify all the various types of movement disorders within a given patient, and to then decide which of these is the dominant one. Some movement disorders occur in relative isolation, such as essential tremor (which may be accompanied by mild ataxia manifested by difficulties in tandem gait or parkinsonism, such as rest tremor or mild cogwheel rigidity), but not by other movement disorders. However, the reality is that many patients manifest a combination of two or

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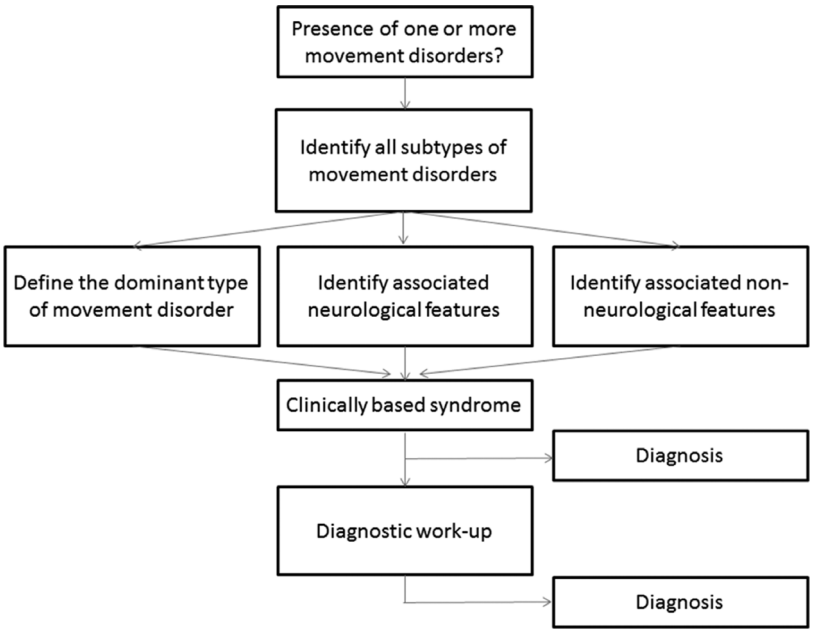

Figure 1.1 Flowchart illustrating the proposed work-up of movement disorders

more movement disorders, and illustrations hereof are abundant. Examples include the presence of dystonia in many patients with hereditary and other forms of parkinsonism or cerebellar ataxia (van Gaalen *et al.* 2011), or the combination of ataxia and myoclonus in Ramsay-Hunt syndrome (Lance 1986). Creutzfeldt-Jakob disease is another example of a mixed movement disorder, characterized by variable combinations of ataxia, myoclonus, and parkinsonism. With careful observation, the presence of multiple concurrent movement disorders is the rule, rather than the exception.

In such patients, it is essential to define which is the dominant movement disorder. This decision is of particular importance as it greatly affects the next phases of the diagnostic process. Indeed, the list of diseases that can be considered are widely different when chorea is the predominant sign, as opposed to when dystonia dominates the clinical presentation. Consequently, the auxiliary tests that can be considered will also differ considerably. Note that "dominant" can be interpreted in two different ways here: either as the movement disorder that is most prominently present (i.e. it "dominates" the clinical presentation, for example, marked and generalized dystonia in a patient with DYT1 dystonia), or as a sign that most markedly affects – and helps to funnel – the diagnostic considerations (i.e. it "dominates" the diagnostic path that is chosen, for example, presence of cerebellar ataxia which, even when subtle, opens the diagnostic ataxia path). The dominant movement disorder will often be the presenting symptom, although this is not necessarily the case.

In the next sections, we will first highlight the characteristic features of the different types of movement disorders, using specific "labels" or "keywords" that may assist clinicians in their clinical pattern recognition. There are two main phenomenological categories that are fairly easy to distinguish: a patient either displays too little movement (hypokinesia) or too much movement (hyperkinesia) (Table 1.1). The first category corresponds to the group of hypokinetic disorders, manifested chiefly by poverty or slowness of movement (bradykinesia), with Parkinson's disease as the classic example. The second group consists of the hyperkinetic movement disorders. This latter group is much more heterogeneous, and may therefore create greater challenges in clinical practice. It helps to separate this hyperkinetic category into two main subdivisions: the first includes movements that have a jerky character; the second includes movements without such a jerky character, but with other characteristic features (namely rhythmicity in tremor, and abnormal posturing in dystonia) (Table 1.1) (Abdo *et al.* 2010). The "jerky" group includes myoclonus, chorea, and tics.

Table 1.1 Classification of movement disorders

Category	Type of movement disorder	Keywords or "labels"
A. Too little movement	Bradykinesia Hypokinesia Akinesia	fatiguing / decrement with repetitive movements; some patients also refer to this motor abnormality as "weakness"; rigidity often accompanies bradykinesia; freezing or motor blocks may be considered examples of akinesia (absence of movement).
B. Too much movement	Jerky – Myoclonus – Chorea – Tics	shock-like; continuous jerk-like movements that flow randomly from one body part to another; tics (motor or phonic) are either simple or complex and are typically preceded by a premonitory sensation or urge; when repetitive they may appear stereotyped; they are often transiently suppressible.
	Non-jerky – Dystonia – Tremor	abnormal posturing, but may be rapid and repetitive (dystonic tremor); rhythmic, oscillatory movement produced by alternating or synchronous contractions of antagonist muscles.

Hypokinetic disorders

A requirement here is to identify the presence of bradykinesia. Bradykinesia is often equated with slowness of movement, or with smaller-than-normal movements. However, bradykinesia is in fact defined by the necessary presence of early fatiguing and progressive decrement of both the speed and amplitude of repetitive movements, such as sequential rapid finger or foot tapping (Abdo *et al.* 2010; Aerts *et al.* 2012). Without such decrement there is no bradykinesia. This is important because slowness of movement occurs as a non-specific sign secondary to dysfunction in many brain circuitries – for example, in patients with weakness, rigidity, or spasticity ("pyramidal slowing") or as a form of compensation (for example, in patients with ataxia who move more slowly to minimize dysmetria). Irregularity of movements or clumsiness is not sufficient to fulfill the criterion of 'bradykinesia' (Daniel and Lees 1993). Indeed, patients with cerebellar ataxia, for example, often also exhibit irregular movements, but lack the classical decrement that is characteristic for true bradykinesia. Depressed patients may also move less or more slowly, but again the decrement in their repetitive movements is missing.

When bradykinesia has been identified convincingly, then the large group of hypokinetic disorders, often associated with rigidity, hence the term "hypokinetic-rigid disorders," can be considered as the underlying explanation. Deciding which of the many hypokinetic-rigid disorders is at play in any given patient depends of course on steps 2 and 3 of the diagnostic process. Generally speaking, the group of hypokinetic-rigid disorders includes Parkinson's disease (PD) (Videos 1.1 to 1.3), including the many genetic variants, and the group of look-alikes that are often bundled under the umbrella term "atypical parkinsonism" (AP). This latter group of AP includes, among others, multiple system atrophy (MSA), progressive supranuclear palsy (PSP) (Video 1.4), dementia with Lewy bodies (DLB), vascular parkinsonism and corticobasal degeneration (CBD) (Videos 1.5 and 1.6).

The definition of PD is likely to change in the foreseeable future (Stern *et al.* 2012). For the time being, it is practical to define "parkinsonism," which according to the conventional core UK Brain Bank criteria includes bradykinesia and at least one of the following: rigidity, rest tremor, or postural instability (Daniel and Lees 1993). A diagnosis of possible PD is then reinforced by the presence of one or more supportive signs, such as asymmetry at onset and during the later course of the disease, or a convincing and sustained response to levodopa. A classical, asymmetric pill-rolling rest tremor also suggests (but does not prove) the presence of PD, as we shall discuss in more detail in the tremor section. Besides classification of PD according to age at onset (young versus late onset), PD may be categorized according to clinical subtypes as either the tremor-dominant form of PD or postural-instability-gait-difficulty (postural instability gait disorder (PIGD)) form of PD. The former generally has a slow progression and favorable response to

medications, whereas the PIGD form of PD tends to progress more rapidly and may be more likely associated with cognitive decline (Jankovic 2008; Stebbins *et al.* 2013).

The various forms of AP also feature bradykinesia, rigidity, postural instability, and often a tremor (and occasionally even a pill-rolling rest tremor), but typically also present with other neurological signs (Fahn *et al.* 2011). These can either consist of other types of movement disorders (such as ataxia or polyminimyoclonus in MSA), but also other neurological or non-neurological signs (such as motor recklessness in PSP, or oromandibular dyskinesias in drug-induced parkinsonism). Concurrent dystonia per se does not help in the differential diagnosis between PD and AP, because many patients with PD (particularly those with a young age at onset) manifest dystonia; exceptions include fixed limb dystonia in CBD and early anterocollis in MSA.

Hyperkinetic movement disorders

Hyperkinetic movement disorders consist of abnormal involuntary movements that have a broad range of phenomenology and etiology (Albanese and Jankovic 2012). Most of the hyperkinetic disorders can be categorized into the jerky and the non-jerky movement disorders (Table 1.1).

Jerky movement disorders

Myoclonus

Myoclonus refers to the occurrence of sudden, brief, and abrupt movements (hence the keyword or label *shock-like*) (Videos 1.7 and 1.8). Physiological myoclonus is exemplified by jerk-like movements experienced by people on the brink of falling asleep (sleep or hypnic jerks). Myoclonic jerks are often 'positive', i.e. caused by muscle contraction, but they can also be 'negative', due to sudden loss of tone, also referred to as asterixis. Negative myoclonus (asterixis) is most characteristically seen in the context of metabolic encephalopathy, such as hepatic or uremic encephalopathy, but can also occur in some neurodegenerative disorders. The startle reflex, consisting of abrupt and often symmetrical movements triggered by sudden (predominantly acoustic) stimuli, is also considered part of the spectrum of myoclonus. Myoclonus can occur spontaneously (at rest), but is also often present – and usually worsened – during movement (action myoclonus), or can be provoked by external tactile or acoustic stimuli (reflex myoclonus and startle responses) (Lozsadi 2012).

There are different ways to classify myoclonus. An important classification method is based on distribution, i.e. focal, multifocal, axial, segmental, or generalized. This distribution pattern is an important clue for the underlying neurological substrate, i.e. cortical, subcortical, brainstem, or spinal. In symptomatic myoclonus, the movement disorder is secondary to other diseases or due to medication. One example is myoclonus as a side effect of medication (for example, morphine, amantadine, serotonin-uptake inhibitors), or the negative myoclonus seen in patients with hepatic and other metabolic encephalopathies.

Chorea

Chorea classically refers to randomly flowing or "dance-like" movements (Videos 1.9 to 1.11). Despite this "elegant" dancing character, each of the individual movements in fact has a jerky nature, but together all these jerks form a constellation of unpredictable and non-rhythmic involuntary movements that flow randomly from one body part to the next. In the examination room, chorea can be difficult to detect, because patients tend to incorporate their choreic movements within their normal movement repertoire (so-called "parakinesia"). This can be especially difficult when chorea is subtle. In such patients, it is important to observe the patient carefully for a prolonged period of time, and to note in particular if the patient conveys a feeling of restlessness to the observer (the "fidgets"). Another challenge is the fact that it is often not the patient who complains, but the family who comment on the fidgety movements of the patient (Walker 2011). Chorea can be become very severe, as exemplified by the sometimes incapacitating levodopa-induced dyskinesias in patients with PD. Marked chorea involving large amplitude movements of proximal limb joints is termed ballism; the term "hemiballism" is used when the ballism is unilateral, involving only one half of the body (Video 1.12). Hemiballism has been described classically as an acute, lateralized sign signaling a subthalamic nucleus infarction, but can also occur with lesions outside of the subthalamic nucleus and as part of the chorea spectrum in many other disorders, including later stages of Huntington's disease. Note that Huntington's disease – which is the classic example of a hyperkinetic movement disorder – also includes bradykinesia as part of the clinical spectrum, and this bradykinesia can even dominate the presentation in young patients (the Westphal variant) or in patients with end-stage Huntington's disease.

A typical associated feature is motor impersistence, which can be identified by asking patients to maintain a certain body position for a prolonged period of time (such as sticking out the tongue, or maintaining a lateralized gaze), or by identifying a fluctuating strength, for example sensing a variable strength of the palmar grip while holding the patient's hand (the so-called "milkmaid's grip").

Tics

The final example of a jerky movement disorder is formed by tics. Like myoclonus and chorea, tics are abrupt and sudden, but tics can be distinguished from myoclonus and chorea based on two different characteristics: tics are largely suppressible, at least for a short time, and they are typically preceded by an urge or rising discomfort that is relieved by performing the actual movement (Fahn *et al.* 2011).

Tics can be divided into simple or complex tics. Simple motor tics (for example, blinking, facial grimacing, shrugging of shoulders) and simple phonic tics (for example, sniffing, throat clearing) typically involve only a single muscle or regional group of muscles (Video 1.13). In contrast, complex motor tics include several groups of muscles in a coordinated, sequential pattern (for example, jumping, skipping) and complex phonic tics result in semantically meaningful utterances (for example, swearing using obscenities or profanities, referred to as "coprolalia") (Video 1.14). One of the most characteristic features of tics, which differentiates this jerk-like movement from other myoclonus and chorea, is the presence of premonitory sensations (Jankovic and Kurlan 2011). Interestingly, tics can be easily overlooked in the examination room, as the patient often consciously or subconsciously suppresses the tics during the doctor's visit. It may be valuable to observe the patient in the waiting room, and especially while the patient is walking back after the visit (Zinner and Mink 2010). Videotaped recordings of patients sitting in front of the camera without a doctor present can also be helpful.

Non-jerky movement disorders

Dystonia

The following is a description of dystonia based on a "consensus" statement (Albanese *et al.* 2013): "Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation." However, dystonia itself is by no means static, and is often accompanied by movements, for example a tremor or other less rhythmic movements within the same body part. Such an irregular tremor is called a "dystonic tremor." The tremor can also occur in body parts other than the ones affected by dystonia. For example, about 25 percent of patients with cervical dystonia have postural tremor in their hands, but it is not clear whether that hand tremor represents coexistent essential tremor or some other tremor. Dystonia may be considered as an example of abnormal sensory-motor integration in the brain, as this helps to explain some relatively unique features of dystonia (Patel *et al.* 2013).

Dystonia may be classified according to anatomic distribution into focal, segmental, generalized, and unilateral (hemidystonia). Focal dystonia often starts as a task-specific movement or posture. Writer's cramp, for example, occurs exclusively during writing and not while performing other tasks with the affected hand (Video 1.15). Other forms of such task-specific dystonia include golfer's cramp and musician's cramp (Ashoori and Jankovic 2008; Dhungana and Jankovic 2013). Such forms of dystonia can be more difficult to demonstrate in the examination room, but it can be helpful to ask the patient to bring along the device that provokes the complaints, such as a golf club or musical instrument, and to demonstrate what happens during the particular activity. Other forms of dystonia may not be exclusively task-specific, but can still manifest a variable degree of severity depending on the specific task, and many forms of dystonia vary in intensity depending on the specific position of the affected body part. Examples include a worsening of jerks when patients rotate their head away from the direction towards which the dystonic muscles are pulling the head, or a variation in dystonic intensity in the hands when patients are asked to slowly rotate their outstretched hands. Another striking example of task-specificity relates to gait, which can be severely affected by dystonia, but with surprisingly fewer problems during running or walking backwards. Besides task-specific dystonia, there are examples of task-specific tremor, such as primary writing tremor. Indeed, an overlap between task-specific tremor and dystonia is suggested by a case report of a patient with unilateral writing tremor (without dystonia), who later developed a true writer's

cramp in the other hand (Pita Lobo *et al.* 2013). One characteristic element of dystonia is the beneficial effect of a sensory trick (such as a gentle touch to the affected body part), which can markedly alleviate the dystonic manifestation. Another feature of dystonia is the development of abnormal posture or movement with voluntary activity of the contralateral body part, the so-called "mirror dystonia" (Video 1.15).

Examples of segmental dystonia include cranial-cervical dystonia, manifested by blepharospasm, oromandibular dystonia, and cervical dystonia (Videos 1.16 and 1.17). Usually idiopathic, this form of dystonia, termed tardive dystonia, may occur as a result of exposure to dopamine-receptor blocking drugs (neuroleptics). Tardive dystonia also typically involves the trunk and upper limbs (Video 1.18). DYT1 dystonia, an autosomal dominant dystonia of childhood-onset, is an example of generalized dystonia (Video 1.19).

The term athetosis was reintroduced by John Morris in an account describing several characteristic cases that fulfilled the original historical descriptions of this phenomenon (Morris *et al.* 2002). Although athetosis is sometimes classified as a form of dystonia, it also has the characteristics of slow chorea in that the slow, wringing, predominantly distal movements are not patterned, which is the characteristic feature of dystonia, but are unpredictable in their direction and character.

In daily clinical practice, three factors help to refine the clinically based differential diagnosis and to guide the diagnostic path: the distribution of the dystonic signs (focal, multifocal, segmental, hemidystonia, or generalized); the age at onset; and the presence of other neurological or non-neurological features (Albanese *et al.* 2013). Commonly used etiological categories include primary, secondary, and dystonia-plus syndromes. Primary dystonia, such as writer's cramp, is often pure and, besides tremor, is not accompanied by other movement disorders. In contrast, dystonia-plus syndromes are typically accompanied by other neurological signs and symptoms, mostly myoclonus and parkinsonism. Secondary dystonia can be seen in the context of a wide array of focal or more generalized brain lesions, such as stroke, demyelinization, and neurodegeneration with brain iron accumulation (NBIA) (Klein and Ozelius 2002; Ozelius *et al.* 2011; Schneider *et al.* 2013).

Tremor

Tremor is characterized by rhythmic, alternating (oscillatory) movements that can involve almost any body part, including the head, chin, arms, and legs. Although the key descriptor is "*rhythmic*," this rhythmicity can be difficult to observe with the naked eye, because variations in tremor amplitude can create a seeming irregularity. Tremor can also be distinguished based on its frequency, but this is not very helpful in clinical practice, because frequencies are difficult to estimate with simple clinical observation. Moreover, the frequency spectra overlap considerably across the various tremor syndromes. In difficult cases, tremor recording, using clinical neurophysiological techniques (EMG, accelerometers, or both), can help to identify true rhythmicity (or multiple co-existent rhythms) and to determine the frequency (Deuschl *et al.* 1998; Elble and Deuschl 2011).

Tremor is usually classified according to the situation in which the tremor occurs. Rest tremor is defined as a tremor occurring in a limb that is completely at rest, hence, it can only be established with certainty if the limb is completely supported against gravity and not moving actively. Voluntary movements often diminish the rest tremor, and sometimes the tremor fully disappears. However, after assuming a new posture, the rest tremor can re-appear with a small delay, and this has been termed the re-emergent tremor (Jankovic *et al.* 1999). This re-emergent rest tremor, which has the same frequency (about 4 to 6 Hz) as the rest tremor, must be distinguished from a postural tremor, which appears immediately after assuming a new posture. Action tremor appears with voluntary movements, and can be divided into postural tremor, kinetic tremor, and intention tremor. The differentiation between kinetic tremor and intention tremor lies in the amplitude of the tremor in the course of the movement trajectory. With intention tremor, the amplitude increases when approaching the target, whereas in kinetic tremor the amplitude remains fairly constant throughout the trajectory. Postural tremor is exemplified by essential tremor, an autosomal dominant tremor involving the hands, head (neck), face, voice, trunk, and legs that typically improves with alcohol and beta blockers (Video 1.20). A special category is orthostatic tremor, which is a high frequency (15 to 20 Hz) tremor of the legs that occurs when standing still, and which causes a subjective and progressive sense of instability. This instability typically – but not always – disappears when the patient starts walking, even though the tremor can still be detected using EMG during walking (Williams *et al.* 2010). This tremor has a fine amplitude and may

not be seen but can be palpated or auscultated with a stethoscope. It can be heard as a characteristic "helicopter sound" in any muscle that acts against gravity (so also in the triceps brachii muscle when the subject is supporting the body weight with the arms). The last category is psychogenic tremor, which is characteristically inconsistent, sensitive to distraction, and which varies in frequency when the subject is asked to make rhythmic movements with other body parts (the psychogenic tremor adopts the voluntarily imposed tremor frequency, 'entrainment') (Edwards and Bhatia 2012; Hallett *et al.* 2011).

In addition to the above-described tremors, there is a group of disorders that can be associated with slow tremor (1 to 3 Hz). These include Holmes' tremor, associated with lesions in the cerebellar outflow pathways, and myorhythmia, manifested by slow tremor in the face (as seen typically in Whipple's disease) or limbs, suggestive of brainstem pathology, as in anti-NMDA receptor encephalitis (Baizabal-Carvallo *et al.* 2013).

Other movement disorders

In addition to the above disorders, there are several others that should be considered in the differential diagnosis. These include stereotypies, such as seen in tardive dyskinesia (Waln and Jankovic 2013; Video 1.21), peripherally induced movement disorders, such as hemifacial spasm (Yaltho and Jankovic 2011; Video 1.22), and paroxysmal dyskinesias (Bhatia 2011).

The second step: from movement disorder to differential diagnosis

The second step is to proceed from the set of identified movement disorder, based largely on phenomenology, to the differential diagnosis. Taken together, the pattern of one or more movement disorders, plus the associated symptoms and signs, will lead to a clinically based (differential) diagnosis based on overall pattern recognition.

For example, patients with ataxia telangiectasia may demonstrate not only ataxia, but also a variety of other movement disorders in addition to telangiectatic vessels in the eyes, multiple carcinomas, and recurrent infections. Another illustrative example was discovered recently, in a clinically based description consisting of a combination of early-onset ataxia, myoclonic seizures, skeletal deformities (in particular scoliosis), and a mildly elevated plasma CK. As it turns out, this specific 'syndrome' fits with a diagnosis of North-Sea myoclonus, caused by mutations in the Golgi SNAP receptor complex 2 gene (GOSR2) (Corbett *et al.* 2011). Another example is the expanding group of disorders categorized as NBIA, which can be manifested by childhood- or adult-onset hypokinetic or hyperkinetic movement disorders (Dusek *et al.* 2012).

The third step: further narrowing the differential diagnosis or proving the diagnosis

The combined results of the first two steps can sometimes be a specific constellation of signs and symptoms that may lead directly to a diagnosis by pattern recognition. There are cases where no diagnostic tests are needed, for example in a patient presenting with a slowly progressive, asymmetrical hypokinetic-rigid syndrome, with a classic pill-rolling rest tremor and an excellent response to levodopa. Most guidelines recommend against routine MRI brain scans in patients presenting with otherwise typical Parkinson's disease (Cheng *et al.* 2010).

Often, however, the situation is not so clear-cut and further investigations are necessary to reach the final diagnosis. Examples of tests include laboratory investigations, structural or functional neuroimaging, neurophysiology, or specific genetic tests. Rather than using everything we have at our disposal in a shotgun approach, the ancillary investigations should be guided by the designated dominant movement disorder, as discussed earlier. A multitude of ancillary tests can be requested. For many reasons, tests should be chosen carefully and targeted to the main differential, with an emphasis on potentially treatable conditions such as Wilson's disease. Many tests have incomplete sensitivity and specificity, which we need to be aware of. It is impossible to discuss all possible tests for the entire spectrum of movement disorders and the section below should not be regarded as a diagnostic manual. Rather, we attempt to touch on the important categories of investigations in this area, with specific examples. Finally, we would like to underscore two important diagnostic 'weapons': time (i.e. wait and see how the disease progresses, and

whether new diagnostic signs arise); and treatment response (as in the example of a patient with possible Parkinson's disease).

Laboratory tests

Routine blood tests

Relatively simple laboratory tests include copper and ceruloplasmin levels to screen for Wilson's disease, alpha-fetoprotein for ataxia telangiectasia or its variants, vitamin deficiencies such as vitamin E deficiency in ataxia or B12 in elderly patients with gait disorders, ruling out uremia in case of myoclonus, and creatine kinase for neuroacanthocytosis.

Metabolic screening

Several errors of inborn metabolism can lead to movement disorders. Often, these diseases present in childhood, and usually the phenotype conveys much more than just the movement disorder, including cognitive deterioration and systemic features. One could consider lactate for mitochondrial disorders, cholestanol for cerebrotendinous xanthomatosis, very long chain fatty acids for peroxisomal disorders such as adrenoleukodystrophy, and lysosomal enzymes for Gaucher's disease.

Microbiology

Some central nervous system infections can result in movement disorders, the best known example of which is perhaps Whipple's disease, which requires positive PCRs for *T. whipplei* in blood and CSF (plus in bowel biopsy). Testing for HIV should be considered in case of progressive and poorly understood neurodegeneration.

Immunological tests

Antibody screening should particularly be considered in cases of more subacutely developing movement disorders. In addition to the "classic" paraneoplastic antibodies, an increasing number of other antibodies is being identified in immune-mediated central nervous system diseases, often non-paraneoplastic. These include, for example, anti-VKGC and anti-NMDA antibodies. Anti-GAD antibodies are associated with stiff person syndrome (Video 1.23). Positive antibodies against thyroid peroxidase (TPO) point to a diagnosis of Hashimoto encephalopathy (or SREAT) in the setting of subacute ataxia and myoclonus. Lastly, celiac disease can be complicated by ataxia and chorea. Laboratory screening includes checking for antibodies against gliadin, endomysium, and tissue transglutaminase (Baizabal-Carvallo and Jankovic 2012).

Cerebrospinal fluid analysis

CSF examination can rule out a central nervous system infection when suspected, and 14–3–3 protein and tau levels are required when Creutzfeldt-Jakob disease is considered. Studies also suggest that analyzing cerebrospinal fluid is of added value in the context of differentiating between the degenerative parkinsonian disorders. In PD, CSF biomarkers are generally within the normal range, while in MSA, CSF levels of tau protein, phospho-tau protein, and the neurofilaments are elevated. In PSP, only the neurofilaments might be slightly raised. In DLB patients, beta-amyloid-42 concentrations can be lower, whereas the neurotransmitter metabolites are elevated (Aerts *et al.* 2011a; Aerts *et al.* 2011b; Constantinescu *et al.* 2009). However, the utility of CSF studies for the individual patient currently remains very limited.

Genetic tests

The number of gene mutations identified in the various movement disorders has increased tremendously over the past years. At present, the speed at which this occurs is amazingly high due to the availability of next-generation sequencing platforms. Already, there are over twenty genetic subtypes of PD and of dystonia, almost sixty for hereditary spastic paraplegia, and about forty for the dominant ataxias. The downside is that it is almost impossible for clinicians to keep track of these developments. Also, current classification systems are flawed and not suitable for selecting the appropriate genetic tests (Marras *et al.* 2012). While we are still mostly requesting a limited number of molecular tests (with traditional Sanger sequencing), some labs already offer parallel sequencing of many genes at once (in packages for a specific movement disorder, for example "ataxia") or even diagnostic exome sequencing. This will very soon change our approach to patients with a (suspected) movement disorder and genetic tests such as whole exome of genome sequencing will be performed at earlier stages in the diagnostic work-up.

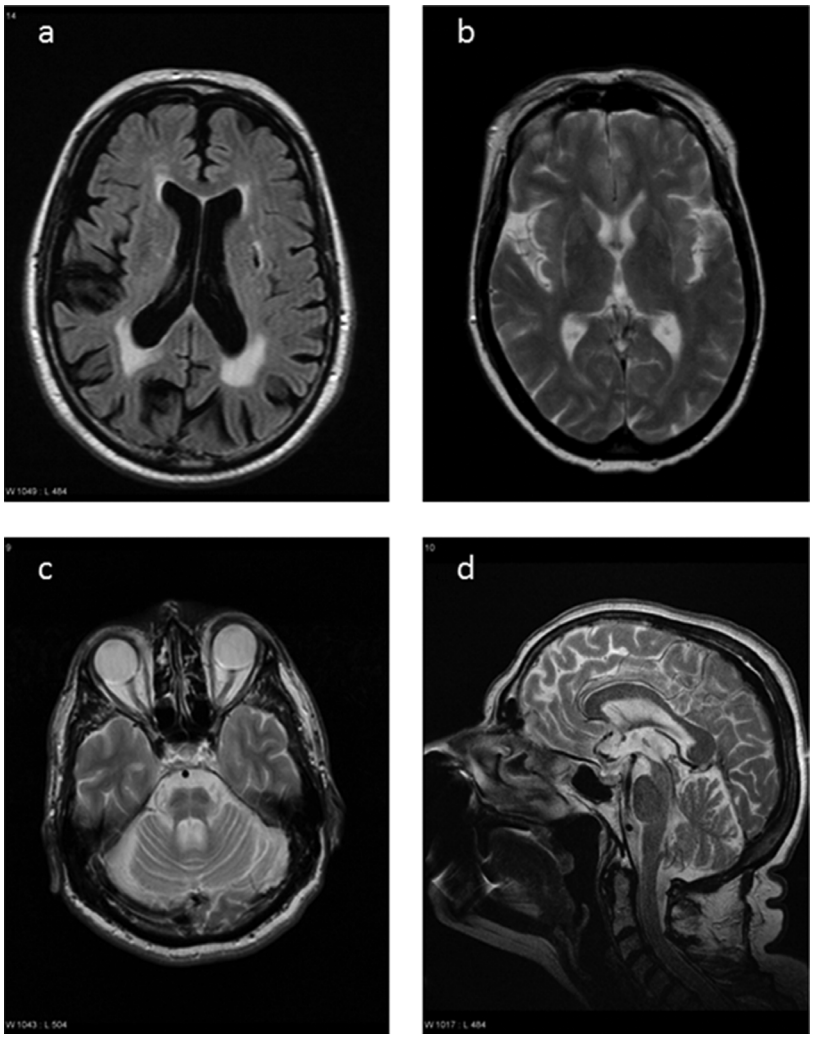

Figure 1.2 MRI images – axial and sagittal. (a) Axial flair image depicting white matter lesions and cortical atrophy in a patient with vascular parkinsonism; (b) axial T2 image depicting a putamenal rim on both sides in a patient with MSA; (c) axial T2 image demonstrating the "hot cross bun sign" in a patient with MSA; and (d) sagittal T2 image showing midbrain atrophy with the "hummingbird" sign in a patient with PSP. *Source*: MRI images kindly provided by F. J. A. Meijer, MD.

Neuroimaging

Neuroimaging is often the very first step in the diagnostic work-up, and the first purpose is to rule out (or demonstrate) that the movement disorder is caused by structural abnormalities. Examples include a cerebellar tumor causing ataxia, a pallidal infarction leading to contralateral hemidystonia, extensive vascular white matter lesions in lower body parkinsonism (Mehanna and Jankovic 2013a) (Figure 1.2a), demyelinating diseases associated with movement disorders (Mehanna and Jankovic 2013b), and NBIA (Dusek *et al.* 2012; Schneider *et al.* 2013).

Secondly, neuroimaging might show abnormalities that are specific for a disease or a limited number of diseases. We have enumerated some of these MRI abnormalities in Table 1.2 (Mahlknecht *et al.* 2010). More advanced techniques include diffusion weighted imaging and diffusion tensor imaging. These techniques may detect changes in the microstructural integrity of nervous tissue earlier than conventional T1- or T2-weighted MRI. Studies have demonstrated that based on the regional apparent diffusion coefficient (ADC), MSA-P and PSP (Nicoletti *et al.* 2006; Paviour *et al.* 2007), PSP and PD (Nicoletti *et al.* 2008), and MSA-P and PD (Köllensperger *et al.* 2008) can be discriminated, although overlapping ADCs have also been described, which questions the utility for the individual patient (Nicoletti *et al.* 2006; Seppi *et al.* 2003).

Table 1.2 Examples of movement disorders with rather specific features on conventional brain MRI

Disease	Feature	Caused by
Huntington's disease		Atrophy of the caudate nucleus
Pantothenate kinase-associated neurodegeneration (PKAN)	Eye-of-the-tiger	Bilateral T2-hypointensity of the medial globus pallidus (iron) with symmetric hyperintensities (cystic changes) in the center thereof
Wilson's disease	Face of the giant panda	More pronounced low intensity of the red nuclei and substantia nigra caused by abnormal hyperintensity of the surrounding tissue within the midbrain tegmentum (on T2)
Parkinson's disease	None	None
Multiple system atrophy	Pallidal hypointensity and putaminal hyperintense rim Hot cross bun sign Other	Darkened putamen (due to atrophy) with linear hyperintensity of the lateral border (T2) (Figure 1.2b) Cruciform hyperintensity within the pons caused degeneration of ponto-cerebellar fibers (T2) (Figure 1.2c) Cerebellar atrophy Abnormal signal in the middle cerebellar peduncle (T2)
Progressive supranuclear palsy	Midbrain>>pons atrophy, "Hummingbird," "Penguin," or "morning glory" sign Other	Atrophy of the midbrain with relatively preserved volume of the pons (sagittal T1/T2) Reduced midbrain diameter on transverse images (Figure 1.2d) Thinning of superior cerebellar peduncles
Corticobasal degeneration		Asymmetric cortical atrophy
Parkinsonism due to manganese intoxication		High T1-signal of bilateral pallidum

Functional imaging

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are scintigraphic techniques to visualize the neurotransmitter systems in the brain. With this approach, we can quantify the integrity of the dopaminergic system, the most common application of these techniques in the movement disorder field.

The post-synaptic part can be visualized with an IBZM-SPECT scan, whereas the pre-synaptic trajectory can be visualized with SPECT scans using dopamine transporter (DAT) ligands such as [^{123}I] beta-CIT, [^{123}I]FP-CIT, or [^{99m}Tc]-TRODAT-1, and/or F(18)-DOPA-PET or ^{11}C raclopride-PET scans (Figure 1.3). In PD, as well as in the other degenerative parkinsonian disorders, there is a loss of dopaminergic neurons in the substantia nigra, and such scintigraphic images will not distinguish between these etiologies. When the differential includes vascular parkinsonism, dystonic tremor, essential tremor, or drug-induced parkinsonism, such scans are useful as these are normal in these diseases. Table 1.3 lists whether DAT scan is abnormal in a variety of movement disorders (Brooks 2010).

Clinical neurophysiology

First, polymyographic recording with surface electrodes can assist in differentiating between some of the hyperkinetic movement disorders (for example, tremor versus myoclonus) and between organic and psychogenic movement disorders (for example, demonstrating entrainment in psychogenic tremor), and can sometimes actually prove a diagnosis (for example, a 15 to 20 Hz leg tremor during standing – orthostatic tremor). Secondly, neurophysiological measurements can further explore the neuroanatomical origin of a movement disorder, for example, distinguishing between a cortical, brainstem, spinal, or psychogenic myoclonus. In cortical myoclonus, one would expect short EMG bursts (less than 50