Chapter 1

General introduction and aims of the thesis

FALLS

"Some two days after my arrival, I saw a boy staggering through the streets. He fell, stopped and fell again." (Negrette A. Personal communication 2001 to 2003)[1] This was the first encounter in 1952 of Amerigo Negrette, a Venezuelan doctor, with a person with Huntington's disease (HD) (Box 1.1) in Maracaibo, Venezuela. In this region a large population is affected by HD. These large kindred played an important role in unraveling the gene that caused this disease.

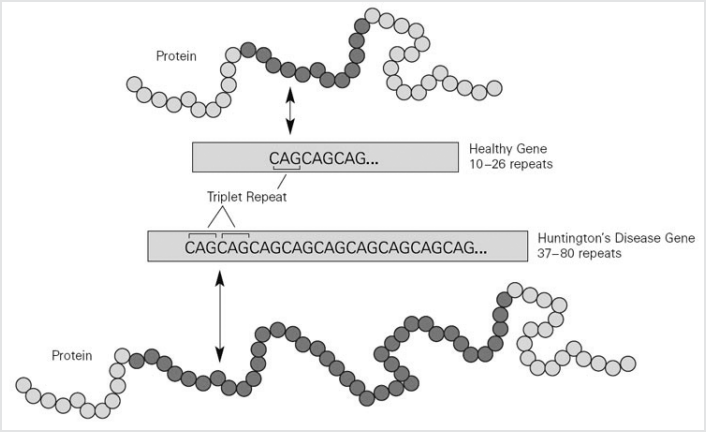
Falls are common in many neurological diseases, including Parkinson's disease (PD) (Box 1.2) and HD.[2,3] These movement disorders share symptoms such as rigidity, bradykinesia, chorea (in HD as part of the disease itself, in PD as a side effect of dopaminergic medication) and postural instability. In both diseases, gait gradually becomes unstable, and postural instability increases as the disease progresses. This almost inevitably leads to falls, frequently with devastating consequences. In the elderly, falls are associated with fractures, hospital admission and nursing home placement.[4,5,6] Next to these sequelae, fallers may also develop an incapacitating fear of renewed falls, and this may in turn lead to a decreased mobility and a lower quality of life.[7]

Box 1.1

Huntington's disease (HD)

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by motor, cognitive, psychiatric, and behavioral disturbances. The prevalence in the United States and Europe is estimated at 5-10 per 100.000 inhabitants and about 5 times as much persons are at risk of developing the disease.[39] Mean age of onset ranges between 43.7 and 55.8 years[40,41] and mean disease duration is approximately 16 years.[38] In 1993 the gene mutation responsible for HD was identified.[42] The 'interesting transcript 15' (IT15) gene on the short arm of chromosome 4 contains an expanded CAG repeat of 36 or more repeats in affected individuals. A repeat of 36-40 is considered as incomplete penetrance, 40 or more repeats invariably lead to symptomatic disease. The length of the CAG repeat plays a role in disease onset leading to an earlier onset for subjects carrying longer repeats.[43,44]

The gene encodes for a protein called huntingtin, and the expanded trinucleotide repeat results in a mutant huntingtin protein containing an expanded polyglutamine tract. Since 1993 research is aimed at the function of huntingtin and the damage that is caused by the mutant huntingtin.



from www.nigms.nih.gov

Despite these devastating consequences, relatively little is known about the epidemiology, circumstances and consequences of falls in patients with PD and HD. There are only few studies that reported the incidence of falls in these disorders. Retrospective studies reported high fall rates, up to 83% in patients with PD[8,9] and 85% in HD.[2] The circumstances and risk factors for falls in these patient groups were not described in detail. Therefore, we prospectively studied the incidence of falls in both diseases, aiming to gain more detailed insight into the potential risk factors and circumstances of these falls (Chapter 3).

The pathophysiology underlying falls is complex and multifactorial, and typically involves combinations of both 'extrinsic' (environmental) factors and 'intrinsic' (patient-related) factors.[10] Examples of extrinsic risk factors include loose rugs or other obstacles on the floor, the presence of stairs in the house, or a cat that wanders about the house. Intrinsic risk factors include, for example, underlying balance impairment, orthostatic hypotension, or violent dyskinesias that may literally perturb the patient beyond the limits of stability. Some of these intrinsic risk factors are specific for PD (e.g. freezing of gait), but patients may also fall due to 'generic' risk factors for falls that would apply to any elderly person. Examples of such generic risk factors include the use of alcohol, visual impairment or the use of sedative medication (in particular benzodiazepines). After mapping all of these intrinsic and extrinsic risk factors, it is possible to develop an individually tailored prevention program that aims to prevent future falls and to reduce the risk of the associated complications (such as fall-related injuries, or a secondary fear of falling).[11]

Box 1.2

Parkinson's disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative disorder. Its cardinal motor features include a resting tremor, rigidity, bradykinesia and postural disturbances. It also encompasses a wide range of non-motor symptoms, such as mood disorders, autonomic dysfunction, olfactory loss and cognitive decline. Some of these non-motor symptoms typically develop in later stages of the disease. Presence of prominent postural instability or severe cognitive disturbances early in the course of the disease is not characteristic for PD and points to the presence of a form of aypical parkinsonism, such as PSP or vascular parkinsonism. The estimated prevalence in Europe is 160 per 100.000 inhabitants.[45] Mean age at onset is approximately 58 years and the prevalence of PD increases with age rising to 360 per 100.000 for those aged 80-84.

The cause of PD remains largely unknown, but genetic and environmental factors are thought to play a role.[46,47] The histological hallmarks of PD are a loss of dopaminergic neurons in the substantia nigra and cytoplasmatic inclusions termed Lewy bodies, that are composed principally of alpha-synuclein. Therapy is mainly focused at correcting the central dopaminergic deficit. Dopaminergic medication improves the main motor symptoms, especially rigidity and bradykinesia. However, not all symptoms improve equally well with dopaminergic therapy. For example, the resting tremor and postural disturbances are typically refractory or respond only partly to dopaminergic therapy. A contribution of non-dopaminergic lesions is supposed to underlie these dopa-resistant symptoms. We hypothesize that a noradrenergic deficit may partially underlie postural disturbances in PD. For this purpose, we review the literature on noradrenergic deficits and the locus coeruleus in PD, and discuss the potential role of this nucleus in postural disturbances in PD (Chapter 2).

ASSESSMENT OF PATIENTS AT RISK OF FALLING

History taking

History taking is the first vital element in assessing fall risk and to screen for the presence of balance disorders. Asking about prior falls is crucial, as these are associated with an increased fall risk in the future in elderly populations.[12,13,14,15] However, recall bias because of cognitive impairment may lead to underreporting of the number of falls.[16,17] It is therefore crucial to interview caregivers to fully elucidate balance problems and to obtain an adequate fall history. Prospectively studying the frequency of falls would avoid such recall problems, and is therefore likely more accurate. For this purpose, falls need to be evaluated on a regular and frequent basis, ideally using a combination of standardized retrospective surveys and prospectively documented falls questionnaires to identify the actual fall circumstances. This method was applied in Chapter 3 and Chapter 4.

Another important element of the assessment is to search for any fear of falling (or its counterpart, balance confidence). Fear of falling may even be present in patients without a history of falls[18], and should always be a part of history taking. In this thesis, we have

studied to what extent fear of falling is associated with falls, and how this may affect the patient's quality of life (Chapter 3 and Chapter 5).

Physical examination

Physical examination should include a generic examination (e.g. blood pressure) and a complete neurological examination. For both PD and HD, specific rating scales have been developed. The Unified Parkinson's Disease Rating Scale (UPDRS) and the Unified Huntington's Disease Rating Scale (UHDRS) include severity ratings of disease-specific symptoms, such as rigidity and tremor for PD, or chorea and dystonia for HD.[19,20] These scales are subdivided into different sections and include not only motor aspects, but also cognitive, behavioral, and functional aspects. Both motor scales include gait and balance evaluations, of which the retropulsion test is probably known best, but this is also the most debated balance test.[21,22,23] The retropulsion test is controversial, because it is difficult to execute and evaluate in a standardized manner. Both the test performance and the rating of the test result are hindered by intrarater and interrater differences.

Therefore, one of the study questions in this thesis was to evaluate the reliability of the retropulsion test in identifying fallers, and its ability to predict future fallers (as documented during prospective follow-up). Furthermore, we wanted to know whether other tests would be more reliable. Several other balance tests have been developed, and we included the most widely used tests in our evaluation (Chapter 3,4 and 5).

Elderly persons commonly encounter difficulties when they have to perform two tasks at the same time (multi-tasking). The 'Stops walking when talking'-test was introduced as a simple test to screen for such difficulties with multitasking.[24] This test examines the ability of subjects to walk and talk at the same time. Difficulty to perform the test adequately turned out to be a good predictor of future falls in the elderly population, at least when patients had some cognitive decline. Specifically, persons who stopped walking as soon as they started a routine conversation were at substantial risk for developing future falls.[23] This is an easy test that can readily be executed in the outpatient clinic, in fact, it can already be carried out when walking the patient to the examination room. We expected this test to have extra good predictive value for patients with PD, because these patients are known to have difficulties performing multiple motor tasks simultaneously or sequentially due to basal ganglia dysfunction.[25] We therefore studied this 'Stops walking when talking'-test in patients with PD, and analyzed its ability to predict future falls in this population (Chapter 6). Dual tasking itself was an important item of the fall questionnaires, and we hypothesized that this would be a difficult task for both PD and HD patients, and also that dual task impairment would be related to an increased fall risk (Chapter 3 and 4).

Quantative measurements

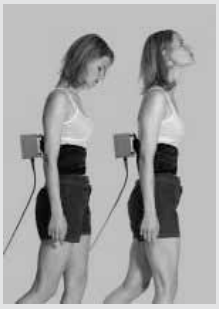
The clinical rating scales described above are all hampered by their subjective nature. Therefore, there is considerable interest in the development of quantitative measurements of gait and balance, hoping that these might offer a more objective perspective on the risk of falls in daily life. Such quantitative studies should investigate both the 'static' and 'dynamic' components of balance. An example of static balance assessment is static posturography, where subjects are quietly standing on a pressure sensitive (but steady) forceplate, which can record spontaneous changes in body sway.[25] An example of dynamic balance assessment is dynamic posturography, where the balance of subjects is actively challenged using either self-inflicted balance perturbations (for example, lifting a weight) or externally induced balance perturbations (for example, the sudden movement after supporting platform upon which subjects are standing).[26] In both cases, the outcome can be objectively recorded using a combination of full body kinematics, surface reactive forces under the feet or surface electromyography. Both techniques have been used quite extensively to evaluate the nature of balance disorders in both PD and HD[21,27,28,29,30,31], although it has thus far proved difficult to correlate these qualitative findings to the problems experienced by patients in daily life.

Next to these qualitative balance studies, several methods have been developed to analyze gait in more detail. This includes comprehensive laboratory-based approaches, where subjects are instructed to walk on a motorized treadmill, and where gait details can be studied in detail using full body kinematics, surface reactive forces under the feet or surface electromyography. Examples of outcome measures include qualitative documentation of step length, step time, walking velocity or the width of the base of support. A specific new development is the use of body-worn accelerometers, that can be used to quantify gait in freely moving subjects.[32,33,34,35] In this thesis, we have used this technique in combination with a pressure sensitive walkway to objective measure several basic gait and balance parameters in freely moving patients with HD (box 1.3) (Chapter 4). Specifically, we wanted to explore the relationship between the documented gait characteristics and the risk of falls in daily life. We expected that studying any differences in gait parameters between fallers (persons who experienced two or more falls in the past year) and non-fallers could identify gait disturbances that were associated with an increased fall risk in HD (Chapter 4).

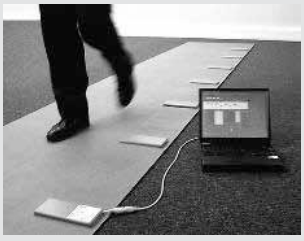
Box 1.3

Accelerometry and electronic walkway.

Assessment of balance control during dynamic tasks can be performed with angular velocity transducers worn on the trunk (Swaystar system, Balance Int. Innovations GmbH, Switzerland).[48] These sensors can measure angular deviations from the centre of mass (COM) in the pitch (anterior-posterior) and roll (lateral) plane during walking without interfering with natural body movements.



Gait disturbances can be quantified using an electronic pressure sensitive walkway that records each footfall as a function of time (GAITRite, CIR Systems, Inc.:Havertown, PA). Outcome measures are spatial and temporal gait parameters such as step length, step time, walking velocity or the base of support. The GAITRite has shown a high validity and reliability in analyzing gait in HD.[49,50]



QUALITY OF LIFE

Do recurrent falls affect the quality of life of patients with movement disorders? In various earlier studies, falls were associated with a lower quality of life in patients with PD.[36,37,38] It is difficult to differentiate between the impact of falls themselves, versus the various factors that are associated with recurrent falls. Disease progression, fear of future falls, injuries or immobilization may all play a role in reducing the patient's quality of life. Therefore, we evaluated the quality of life in PD patients in relation to previous falls and other fall-related factors (Chapter 5).

PREVENTION OF FALLS

The consequences of falls can be devastating for patients with movement disorders. It is therefore crucial to prevent falls in this vulnerable population. As the pathophysiology of falls is multifactorial, any therapeutic approach should include an integrated intervention program aimed at all of the different factors that play a role. A first crucial step is to map all of the intrinsic and extrinsic risk factors that might contribute to the risk of falls for each individual patient. Both generic and disease-specific risk factors should be identified. Only then is it possible to develop an individually tailored prevention program that aims to prevent future falls, and to reduce the risk of the associated complications (such as fall-related injuries, or a secondary fear of falling). The other important goals of such intervention programs should be the preservation of mobility and independence. There is currently no program that describes the development of an individually tailored intervention. We have therefore reviewed all potential risk factors in PD (both generic and disease-specific; and both 'extrinsic' and 'intrinsic'), and propose a multifactorial intervention program to prevent future falls in this population (Chapter 7).

SPECIFIC AIMS OF THE THESIS

This thesis describes the impact of balance disturbances on patients with either PD or HD, and aims to provide better insight into the assessment of risk factors of falls in these two patient groups, as a basis for falls prevention and improvement of the quality of life. The main goals of this study were as follows:

1. To review the neuropathological changes underlying falls in PD, with specific emphasis on the possible role played by the locus coeruleus and the associated changes in noradrenergic neurotransmission (Chapter 2).
2. To prospectively study the epidemiology of falls in PD and HD (Chapter 3 and 4).
3. To gain better insight into the pathophysiology of falls in PD and HD, and to assess potential risk factors of falls (Chapter 3,4 and 6)
4. To evaluate the impact of falls on the quality of life for patients with PD (Chapter 5).
5. To develop a multifaceted prevention program to reduce falls in PD (Chapter 7).

REFERENCES

1. Okun MS, Thommi N. Americo Negrette (1924 to 2003): diagnosing Huntington disease in Venezuela. Neurology.2004;63:340-343.
2. Koller WC, Trimble J. The gait abnormality of Huntington's disease. Neurology 1985;35:1450-1454.
3. Stolze H, Klebe S, Zechlin C et al. Falls in frequent neurological diseases--prevalence, risk factors and aetiology. J Neurol. 2004;251:79-84.
4. Spaniolas K, Cheng JD, Gestring ML et al. Ground level falls are associated with significant mortality in elderly patients. J Trauma 2010;69:821-825.
5. Tinetti ME, William CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med. 1997;337:1279-1284.
6. Woolcott JC, Khan KM, Mitrovic S et al. The cost of fall related presentations to the ED: A prospective, in-person, patient-tracking analysis of health resource utilization. Osteoporos Int. 2012;23: 1513-1519.
7. Bloem BR, van Vugt JP, Beckley DJ. Postural instability and falls in Parkinson's disease. Adv Neurol. 2001;87:209-223.
8. Koller WC, Glatt S, Vetere-Overfield B et al. Falls and Parkinson's disease. Clin Neuropharmacol. 1989;12:98-105.
9. Wenning GK, Ebersbach G, Verny M et al. Progression of falls in postmortem – confined parkinsonian disorders Mov Disord. 1999;14:947-950.
10. Voermans NC, Snijders AH, Schoon Y et al.Why old people fall (and how to stop them). Pract Neurol. 2007;7:158-171.
11. Bloem BR, Geurts AC, Hassin-Baer S et al. Treatment of gait and balance disorders. In:Therapeutics of Parkinson's disease and other movement disorders, edited by M. Hallett and W.H. Poewe, Chichester:John Wiley & Sons, Ltd, 2008:417-443.
12. Ashburn A, Stack E, Pickering RM et al. Predicting fallers in a community-based sample of people with Parkinson's disease. Gerontology 2001;47:277-278.
13. Ganz DA, Bao Y, Shekelle PG et al. Will my patient fall? JAMA. 2007;297:77-86.
14. Stel VS, Pluijm SM, Deeg DJ et al. A classification tree for predicting recurrent falling in community-dwelling older persons. J Am Geriatr Soc. 2003;51:1356-1364.
15. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med. 1988;319:1701-1707.
16. Cummings SR, Nevitt MC, Kidd S. Limited accuracy of recall of falls in the elderly. J Am Geriatr Soc. 1988;36:613-616.
17. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. J Am Geriatr Soc 2005;53:2190-2194.
18. Scheffer AC, Schuurmans MJ, van Dijk N et al. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. Age Ageing 2008;37:19-24.
19. Kieburtz K, Penney JB, Como P et al. Unified Huntington's disease rating scale: Reliability and consistency. Mov Disord 1996; 11:136-142.
20. Lang AE. Clinical rating scales and videotape analysis. In: Therapy of Parkinson's disease. Second Edition. Edited by Koller WC, Paulson G, editors. New York: Marcel Dekker Inc New York 1995.
21. Bloem BR, Beckley DJ, van Hilten BJ et al. Clinimetrics of postural instability in Parkinson's disease. J Neurol. 1998;245:669-673.
22. Hunt AL, Sethi KD. The pull test: a history. Mov Disord 2006;21:894-899.
23. Munhoz RP, Li JY, Kurtinecz M et al. Evaluation of the pull test technique in assessing postural instability in Parkinson's disease. Neurology 2004;62:125-127.

24. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. Lancet 1997;349:617.
25. Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. Neurology 1982;35:514-539.
26. Visser JE, Carpenter MG, van der Kooij H et al. The clinical utility of posturography. Clin.Neurophysiol 2008;119:2424-2436.
27. Carpenter MG, Allum JH, Honegger F et al. Postural abnormalities to multidirectional stance perturbations in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:1245-1254.
28. Dimitrova D, Horak F and Nutt JG. Postural muscle responses to multidirectional translations in patients with Parkinson's disease. J Neurophysiol 2004;91:489-501.
29. Earhart GM, Stevens ES, Perlmutter JS et al. Perception of active and passive turning in Parkinson disease. Neurorehabil Neural Repair 2007;21:116-122.
30. Schieppati M, Nardone A. Free and supported stance in Parkinson's disease. Brain 1991;114:1227-1244.
31. Tian J, Herdman SJ, Zee DS et al. Postural stability in patients with Huntington's disease. Neurology 1992;42:1232-1238.
32. Adkin AL, Bloem BR, Allum JH. Trunk sway measurements during stance and gait tasks in Parkinson's disease. Gait Posture 2005;22:240-249.
33. Bachlin M, Plotnik, Roggen MD et al. Wearable assistant for Parkinson's disease patients with the freezing of gait symptom. IEEE Trans Inf Technol Biomed 2010;14:436-446.
34. Chiari L, Dozza M, Cappello A et al. Audio-biofeedback for balance improvement: an accelerometry-based system. IEEE Trans Biomed Eng. 2005;52:2108-2111.
35. Salarian A, Russmann H, Vingerhoets FJ et al. Ambulatory monitoring of physical activities in patients with Parkinson's disease. IEEE Trans Biomed Eng 2007;54:2296-2299.
36. Reuther M, Spottke EA, Klotsche J et al. Assessing health-related quality of life in patients with Parkinson's disease in a prospective longitudinal study. Parkinsonism Relat Disord 2007;13:108-114.
37. Rahman S, Griffin HJ, Quinn NP et al. Quality of life in Parkinson's disease: the relative importance of the symptoms. Mov Disord 2008;23:1428-1434.
38. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;69:308-312.
39. Bates G, Harper PS, Jones L. Huntington's disease. Third edition New York: Oxford University Press Inc 2002.
40. Adams P, Falek A. Arnold J. Huntington's disease in Georgia: age at onset. Am J Hum Genet 1988; 43:695-704.
41. Roos RA, Hermans J, Vegter-van der Vlis M et al. Duration of illness in Huntington's disease is not related to age at onset. J Neurol Neurosurg Psychiatry 1993;56:98-100.
42. The Huntington's disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993;72:971-983.
43. Andrew SE, Goldberg YP, Kremer B et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. Nat Genet 1993;4:398-403.
44. Snell RG, MacMillan JC, Cheadle JP et al. Relationship between trinucleotide repeat expansion and phenotypic variation in Huntington's disease. Nat Genet 1993;4:393-397.
45. De Rijk MC, Tzourio C, Breteler MM et al. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. JNNP 1997;62:10-15.

46. Burbulla LF, Krüger R. Converging environmental and genetic pathways in the pathogenesis of Parkinson's disease. J Neurol Sci 2011;306:1-8.
47. Gasser T. Update on the genetics of Parkinson's disease. Mov Disord 2007;22 Suppl 17:S343-350.
48. Allum JH, Carpenter MG. A speedy solution for balance and gait analysis: angular velocity measured at the centre of body mass. Curr Opin Neurol 2005;18:15-21.
49. Bilney B, Morris ME, Churchyard A et al. Evidence for a disorder of locomotor timing in Huntington's disease. Mov Disord 2005;20:51-57.
50. Rao AK, Quinn L, Marder KS. Reliability of spatiotemporal gait outcome measures in Huntington's disease. Mov Disord 2005;20:1033-1037.