Parkinsonism beyond Parkinson's disease

Atypical Parkinsonism in other sporadic and genetic neurodegenerative diseases

Alzheimer disease (sporadic and genetic)

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Abstract

Alzheimer disease (AD) is a neurodegenerative disease characterized by deposition of pathologically aggregated amyloid-β in the extracellular space and pathologically aggregated tau protein in the intracellular space. Mainly affected brain areas are the temporal and the parietal lobe, which cause the classical AD phenotype consisting of increasing forgetfulness and difficulties to orientate. However, AD pathology is not restricted to these brain areas and spreads through the brain as the disease progresses, which can lead to a number of additional symptoms and to atypical presentations. Motor symptoms in AD are the topic of this chapter. Even though motor symptoms are usually not severe and seldomly treated, motor symptoms are quite frequent and can be observed in the majority of AD cases. Motor symptoms are especially frequent in cases with early onset and long disease duration, for example in Apolipoprotein E e4 carriers and in familial early onset AD. In severe cases treatment with pharmacological approaches might be considered. However, treatment strategies largely rely on expert opinions. Due to potential positive impact on prognosis non-pharmacological treatment and exercise might be considered in less advanced cases.

I. Sporadic Alzheimer disease

Diagnostic criteria

The gold standard for the diagnosis of Alzheimer disease (AD) is the neuropathological finding of a neurodegenerative disease characterized by deposition of pathologically aggregated amyloid-β and tau protein in the context of an appropriate clinical syndrome (1). The clinical diagnosis of sporadic AD (sAD) consists of a diagnostic framework that was initially established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) workgroup. AD criteria were revised multiple times, in 2011 under the guidance of the National Institute on Aging and the Alzheimer's Association (the NIA-AA criteria) (2). These criteria recognize that AD progresses on a clinical spectrum with three defined stages: A preclinical stage with no symptoms, but biomarker-positivity, a stage of mild cognitive impairment (MCI) and a dementia stage. The current 2018 NIA-AA research criteria require the presence of an appropriate clinical AD phenotype (typical or atypical) and a pathophysiological biomarker consistent with the presence of Alzheimer pathology (3). Symptoms of MCI include concern about a change in cognition relative to previous functioning; impairment of one or more cognitive functions, for example memory and problem solving; preserved ability to function independently in daily life, hence, absence of dementia. In the dementia stage impairment of cognitive functions such as memory loss, word-finding difficulties, and visual/spatial problems, have reached the level to impair a person's ability to function independently (2). Motor symptoms are not required for the diagnosis of classical sAD. Biomarker of AD are grouped in categories reflecting distinct aspects of AD pathology, namely amyloid-β deposits, deposits of pathologic tau, and neurodegeneration (4).

Time course, prevalence and consequences of motor symptoms

Patients with sAD often develop motor symptoms during the course of the disease. The majority of these motor symptoms are of a hypokinetic-rigid nature. Cognitive performance and motor symptoms are correlated. Presence of motor symptoms is associated with low cognitive performance and difficulties in activities of daily living (5). In the literature at least some degree of movement disorder has been described in 30 % up to 90 % of all sAD patients (5-9). The prevalence and symptom load of motor symptoms increase with the course of the disease (5-9). However, the overall symptom load usually remains quite low relative to cognitive symptoms. These clinical observations suggest that motor regions of the central nervous system are frequently affected by AD pathology (7). Moreover, presence of motor symptoms is associated with a poor prognosis in sAD. In detail, motor signs, especially postural and gait abnormalities, are associated with increased risk for cognitive decline, functional decline, institutionalization, and death (6, 9). In some cases of sAD the development of movement disorders can precede cognitive

symptoms (7). Special attention to motor symptoms is necessary in case of treatment of sAD patients with neuroleptics. In this scenario a very high proportion of sAD patients show some motor symptoms (5).

Types of movement disorders

In contrast to “classical” forms of typical and atypical parkinsonism the type of parkinsonism developed in sAD is predominated by bradykinesia rather than by rigidity or both. In a detailed study of motor symptoms in sAD more than half of the affected patients showed hypomimia, dysarthria and bradykinesia of limbs. Postural instability and abnormal gait were present in between one third and 50% of the patients. In contrast, rigidity was present in only about one fourth of the patients (5). Hypokinetic motor symptoms tend to deteriorate at a rate of approximately 3% per year (8). Faster rates of motor sign accumulation are associated with faster rates of disease progression in other areas. In contrast, hyperkinetic movement disorders such as different types of tremor (8), dystonia and dyskinesias are rare and deteriorate at a much lower rate than hypokinetic movement disorders (1,8).

Other non-parkinsonian motor symptoms are common in sAD. Patients with sAD are more prone to myoclonus and to seizures. Up to 10% of sAD patients show newly diagnosed epileptic seizures after the diagnosis of AD. Myoclonus is even more frequent and has been observed in up to 50 % of sAD cases throughout the disease course. Both symptoms develop usually a few years after sAD diagnosis and are more frequent in individuals with early onset. There are reports suggesting that epilepsy develops on average approximately 3 years after diagnosis and myoclonus approximately 5 years after diagnosis (10).

Pisa syndrome or pleurothotonus is another movement disorder that is occasionally observed in AD patients. Pisa syndrome consists of a lateral inclination of the trunk while standing or walking and is often associated with treatment with cholinesterase inhibitors (11) and can be reversible upon the cessation of cholinesterase inhibitors (12).

Treatment

In most cases motor symptoms are of minor relevance to the care and well-being of the patients. In case motor symptoms are considered clinically relevant, the medication should be revised for neuroleptics. If present, a discussion of the possibility to end treatment with neuroleptics should follow (7). In terms of medication it has been suggested that levodopa treatment improves the excitability of the motor cortex in sAD (13). In single cases with marked parkinsonism caused by pure AD pathology, treatment with levodopa has shown to be effective (14). This suggests that dopaminergic treatment might be considered in select cases. In the opinion of the author, treatment of motor symptoms with dopaminergic drugs in sAD should follow the suggestions for treatment of

dementia with Lewy bodies (DLB) "*treat low, go slow*". However, recommendations about clinical management of DLB are largely based upon expert opinion since only few randomized controlled trials are available (15). Non-pharmacological treatment options should also be considered. Initial data suggest that interventions with physiotherapy may have benefits on motor symptoms in sAD (16). Exercise and physiotherapy might not only be beneficial in improving on-going motor symptoms, but also improve the prognosis of cognitive function, decrease neuropsychiatric symptoms, and slow decline in activities of daily living (17).

The role of Lewy body pathology in movement disorders in sporadic Alzheimer disease

DLB is a phenotypically and pathologically distinct disease entity consisting of dementia and parkinsonism often associated with REM-sleep behavior disorder, hallucinations, vegetative dysfunction, fluctuations in vigilance and reduced striatal dopamine transporter activity on functional neuroimaging (15). Importantly, patients often show severe sensitivity to neuroleptic drugs. To distinguish patients with LBD from patients with Parkinson's disease dementia (PDD) the one-year rule is applied. The one-year rule refers to the sequence of the occurrence of Parkinsonism and dementia. While DLB as a disease entity is not the topic of this chapter, the relation to sAD is complex, especially in the context of motor symptoms, because it has been reported that approximately half of all patients with the clinical diagnosis of classical sAD show some degree of Lewy body co-pathology (18). In turn, it is not uncommon that patients fulfilling the diagnostic criteria of DLB might be biomarker positive for amyloid-β in CSF or amyloid-PET imaging (15). Even in familial autosomal dominantly inherited AD, where due to the effect of the disease causing mutations the driver of pathology is clearly amyloid-β, a similar proportion of patients like in sAD shows presence of Lewy body co-pathology (19). This poses the question about the role of Lewy body pathology in the presence of motor symptoms in patients with classical late-onset sAD. Detailed retrospective analyses of patients that came to autopsy found a higher proportion of Lewy body co-pathology in sAD patients with motor symptoms. In addition, individuals with Lewy body co-pathology showed a younger age at onset and a younger age at death as well as a higher proportion of apolipoprotein E ε4 allele carriers (18).

Phenotypic variants of sporadic Alzheimer disease with motor symptoms

Corticobasal Syndrome: A proportion of patients with corticobasal syndrome (CBS) (20) show classical Alzheimer pathology as the underlying cause. For details regarding CBS and its phenotypes we refer to the dedicated chapter 4/3c[editor?]. In short, a high proportion of CBS patients with underlying AD pathology in addition to the classical CBS phenotype showed pronounced apraxia, myoclonus and gait disorders. In such cases relevant neuronal loss in the substantia nigra associated with AD pathology was shown (21).

Posterior cortical atrophy: Another phenotypic variant of AD is posterior cortical atrophy (PCA). This syndrome has variable sub-forms which have recently been conceptualized in the new diagnostic criteria of PCA (22). In case of a clinical diagnosis of PCA an underlying AD pathology is not mandatory, but probable. In the new categories of PCA-plus, PCA-CBS has been defined as PCA plus a clinical syndrome fulfilling the current criteria for CBS (20) including limb rigidity or akinesia and/or limb dystonia and/or limb myoclonus (22).

II. Genetic Alzheimer disease

Autosomal dominantly inherited Alzheimer disease

Autosomal dominantly inherited AD (ADAD) is a rare familiar variant of AD with early onset at a mean age of 42 years that is caused by triplications of the amyloid precursor protein (APP)-gene (23) or by mutations in the APP, presenilin-1 (PSEN1) (24) and presenilin-2 (PSEN2) (25) genes. All these mutations have in common that they alter APP processing and hence amyloid-β is the driver of the pathology in ADAD. Interestingly, approximately 50% of ADAD cases show Lewy body co-pathology on autopsy (19). In a recent comprehensive analysis of data from the Dominantly Inherited Alzheimer Network (DIAN) and data from an extensive literature search, parkinsonism was present in approximately 10% of the cases with ADAD. Compared to other motor symptoms in this population the prevalence of parkinsonism was slightly lower compared to spasticity (10-15%) and myoclonus (10-20%). Similar to sAD, motor symptoms were more common at younger age of onset and increased in prevalence in more advanced disease stages (26). A study more focused on motor symptoms showed that the symptom load of Parkinsonism in ADAD is overall mild and dominated by hypokinesia showing only slight signs of rigidity (27). Furthermore, as in sAD motor signs can precede cognitive disease onset. In contrast to sAD, ADAD is characterized by relatively high amounts of amyloid-β deposits in the basal ganglia. It was shown that the quantity of amyloid-β PET signal correlates with the amount of motor symptoms. In advanced disease stages, ADAD mutation carriers seem to have a higher burden of motor symptoms compared to patients with late-onset sAD, which is in line with the fact that motor symptoms seem to be more frequent in individuals with early onset AD.

Apolipoprotein E

Apolipoprotein E (ApoE) e4 genetic status is the strongest genetic risk factor for sAD (28). Findings regarding associations between ApoE status and motor findings are inconsistent. The presence of an ApoE e4 allel is associated with a tendency to have more Lewy body co-pathology which is associated with slightly more motor symptoms in sAD (see above). On the

other hand, an association between ApoE e4 positivity and decreased risk for motor signs in sAD was reported (8). In ADAD, the presence of motor findings was not associated with a distinct ApoE status (27).

Down Syndrome

Due to the localization of the APP gene on chromosome 21 most individuals with Down Syndrome (DS) carry three copies of the APP gene. Similar to individuals with three isolated copies of the APP gene, which leads to autosomal dominantly inherited AD, individuals with DS are at ultra-high risk to develop a genetically determined early onset AD. In contrast to APP triplication ADAD, penetrance seems to be very high but not full (29). AD associated motor deficits have not been studied in great detail in DS. As many individuals with DS have baseline motor symptoms associated with cerebellar hypoplasia and reduced number of granule cells, motor symptoms observed in cross sectional analyses are not easily attributable to the presence of AD (30). However, in a cross-sectional study comparing individuals with DS with and without AD, Parkinsonism has been described in 5% of AD-DS patients and prevalence increased to 10% in late stage AD-DS (31). Hence, like in sAD and ADAD also in AD-DS the prevalence of motor symptoms seems to increase with disease progression (31).

Summary

Motor symptoms are common in AD. In the majority of cases motor symptoms are not severe and are seldomly treated. Motor symptoms are more frequent although rarely very severe in cases with early onset AD and more common in patients with long disease duration. In severe cases treatment with pharmacological approaches can be considered. Medication should be screened for neuroleptics and revised, if possible. Due to potential positive impact on prognosis non-pharmacological treatment options, such as physiotherapy and exercise, might be considered also in less severe cases. Taking into account the earlier onset of genetic forms of AD, motor signs show mainly a bradykinetic profile and are relatively similar in all types of the disease with a classical AD phenotype. However, there are rare phenotypic variants with underlying AD pathology that might present with severe and predominant motor phenotypes, for example with CBS.

References

1. Bharadwaj R, Cimino PJ, Flanagan ME, et al., Application of the condensed protocol for the NIA-AA guidelines for the neuropathological assessment of Alzheimer's disease in an academic clinical practice. Histopathology. 2018 Feb;72(3):433-440.
2. McKhann GM, Knopman DS, Chertkow H, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9.
3. Dubois B, Feldman HH, Jacova C, et al., Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014 Jun;13(6):614-29.
4. Jack CR Jr, Bennett DA, Blennow K, et al., NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018 Apr;14(4):535-562. doi: 10.1016/j.jalz.2018.02.018.
5. Tsolaki M, Kokarida K, Iakovidou V, Stilopoulos E, Meimaris J, Kazis A. Extrapyramidal symptoms and signs in Alzheimer's disease: prevalence and correlation with the first symptom. Am J Alzheimers Dis Other Demen. 2001 Sep-Oct;16(5):268-78.
6. Tosto G, Monsell SE, Hawes SE, Mayeux R. Pattern of extrapyramidal signs in Alzheimer's disease. J Neurol. 2015 Nov;262(11):2548-56. doi: 10.1007/s00415-015-7886-1.
7. Albers MW, Gilmore GC, Kaye J, et al., At the interface of sensory and motor dysfunctions and Alzheimer's disease. Alzheimers Dement. 2015 Jan;11(1):70-98.
8. Scarmeas N, Hadjigeorgiou GM, Papadimitriou A, et al., Motor signs during the course of Alzheimer disease. Neurology. 2004 Sep 28;63(6):975-82.
9. Scarmeas N, Albert M, Brandt J, Blacker D, et al., Motor signs predict poor outcomes in Alzheimer disease. Neurology. 2005 May 24;64(10):1696-703.
10. Beagle AJ, Darwish SM, Ranasinghe KG, La AL, Karageorgiou E, Vossel KA. Relative Incidence of Seizures and Myoclonus in Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia. J Alzheimers Dis. 2017;60(1):211-223.
11. Vanacore N, Suzzareddu G, Maggini M, Casula A, Capelli P, Raschetti R. Pisa syndrome in a cohort of Alzheimer's disease patients. Acta Neurol Scand. 2005 Mar;111(3):199-201.

12. Vöglein PSEN Mutation
13. Martorana A, Stefani A, Palmieri MG, et al., L-dopa modulates motor cortex excitability in Alzheimer's disease patients. Neural Transm (Vienna). 2008 Sep;115(9):1313-9.
14. Kasahata N, Hagiwara M, Kato H, Nakamura A, Uchihara T.An 85-year old male with levodopa-responsive parkinsonism followed by dementia and supranuclear ophthalmoplegia caused by alzheimer-type pathology without Lewy bodies. J Alzheimers Dis. 2014;39(3):471-6.
15. McKeith IG, Boeve BF, Dickson DW, et al., Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017 Jul 4;89(1):88-100.
16. Zhu XC1, Yu Y2, Wang HF1, et al., Physiotherapy intervention in Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis. 2015;44(1):163-74.
17. Cass SP. Alzheimer's Disease and Exercise: A Literature Review. Curr Sports Med Rep. 2017 Jan/Feb;16(1):19-22.
18. Chung EJ, Babulal GM, Monsell SE, Cairns NJ, Roe CM, Morris JC. Clinical Features of Alzheimer Disease With and Without Lewy Bodies. JAMA Neurol. 2015 Jul;72(7):789-96.
19. Cairns NJ, Perrin RJ, Franklin EE, et al., Neuropathologic assessment of participants in two multi-center longitudinal observational studies: the Alzheimer Disease Neuroimaging Initiative (ADNI) and the Dominantly Inherited Alzheimer Network (DIAN). Neuropathology. 2015 Aug;35(4):390-400.
20. Armstrong MJ, Litvan I, Lang AE, et al., Criteria for the diagnosis of corticobasal degeneration. Neurology. 2013 Jan 29;80(5):496-503. doi: 10.1212/WNL.0b013e31827f0fd1.
21. Sakae N, Josephs KA, Litvan I, et al., Clinicopathologic subtype of Alzheimer's disease presenting as corticobasal syndrome. Alzheimers Dement. 2019 Aug 6. pii: S1552-5260(19)30115-3. doi: 10.1016/j.jalz.2019.04.011.
22. Dickerson BC, Vandenberghe R, Ahmed S, et al., Consensus classification of posterior cortical atrophy. Alzheimers Dement. 2017 Aug;13(8):870-884. doi: 10.1016/j.jalz.2017.01.014. Epub 2017 Mar 2.
23. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in

the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991; 349(6311): 704-6.

24. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995; 375(6534): 754-60.
25. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. Science 1995; 269(5226): 973-7.
26. Tang M, Ryman DC, McDade E, et al., Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the Dominantly Inherited Alzheimer Network observational study (DIAN-OBS). Lancet Neurol. 2016 Dec;15(13):1317-1325.
27. Vöglein J, Paumier K, Jucker M, et al., Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer's disease. Brain. 2019 May 1;142(5):1429-1440.
28. Karch C, Goate A, Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biological Psychiatry. 2015 January; 77:43–51.
29. Wiseman FK, Al-Janabi T, Hardy J, et al., A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. Nat Rev Neurosci. 2015 Sep;16(9):564-74.
30. Ira T Lott, Mara Dierssen. Cognitive defi cits and associated neurological complications in individuals with Down's syndrome. Lancet Neurol 2010; 9: 623–33.
31. McCarron M, Gill M, McCallion P, Begley C. Health co-morbidities in ageing persons with Down syndrome and Alzheimer's dementia. J Intellect Disabil Res. 2005 Jul;49(Pt 7):560-6.
32. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3): 280-92.
33. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013; 12(2): 207-16.

Figure legend:

Figure: Clinical- and biomarker-changes in the course of Alzheimer Disease. The figure is adapted from Jack and colleagues32,33 and aims to show the timeline for the emergence of motor symptoms in relation to cognitive decline and biomarkers for pathological Aβ. The assumption is made that motor symptoms can occur in the cognitive normal phase and in the end stage affect more than 50% of the patients.