Age, comorbidity: frailty in observational and analytic studies of neurological diseases

Jan Novy[a], Josemir W. Sander[b]

[a]Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, CH-1011 Lausanne , Switzerland

[b]NIHR University College London Hospitals Department of Clinical and Experimental Epilepsy, National Hospital for Neurology and Neurosurgery, and UCL Institute of Neurology; 23 Queen Square, London WC1N 3BG, United Kingdom, Epilepsy Society, Chalfont St Peter SL9 0RJ, United Kingdom, Stichting Epilepsie Instellingen Nederland (SEIN), Achterweg 5, 2103 SW Heemstede, The Netherlands

Abstract

Co-morbidities are rarely taken into account in studies of neurological conditions although they may be a confounder of the outcome and treatment. The relationship between co-morbidities and neurological conditions is also biased; the comorbidities may be symptoms of the underlying cause of the neurologic condition or long term adverse effects of the treatment. There is evidence that several common neurological conditions have an increased burden of somatic and psychiatric comorbidities compared with matched samples from the general population. Depression is probably the most common comorbidity. Both psychiatric and somatic comorbidities have been shown to account for some of the premature mortality encountered in these neurological conditions. Comorbidities and age can also be important factors in the response and tolerance to treatment and can alter the general outcome of a disease. Age and comorbidities should not be overlooked in the observation and assessment of neurological conditions and their treatment.

The importance of age and comorbidity has long been recognized as influencing the overall outcome in medical conditions, but little attention has been paid to this aspect in neurological conditions in treatment trials. According to Feinstein's original definition, "the term comorbidity will refer to any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" [1]. Ageing and comorbidity often go together (but not invariably) as the proportion of chronic conditions and multimorbidities in the general population increases with ageing (ref), and this frequently coincides with an increased mortality rate. The comorbidity effect is difficult to consider as a whole because of the heterogeneity of the conditions it encompasses and their interindividual varying severity. The consequences of the overall burden of comorbidities have mostly been studied in the mortality risk field; several scores (such as the Charlson or Elixhauser scores) were developed based on longitudinal observational studies to predict the mortality risk over a period of time for combinations of comorbidities. Each comorbidity is given a weighted score according to the mortality risk observed associated with that comorbidity.

Treatment trials in neurological conditions rarely take comorbidities into account. Treatment trials favour homogenous cohorts, with well-defined age groups and disease severity, and tend to exclude people with problematic comorbidities, to give the greatest likelihood of showing a difference in outcome between comparators. Comorbidities could be confounders in several aspects of treatment trials[1]. As seen most obviously in studies where the outcome is survival, serious unrecognised comorbid conditions (such as cardiovascular diseases) can interfere with the results of the treatment trial. If comorbidities lead the individual to consult a physician, however, it is possible that the first signs of the studied disease, still unnoticed by the individual, could be identified and the diagnosis of the disease made earlier than usual in the natural history. If the comorbid condition's prognosis is poor, this may also bias the choice of treatment of the condition studied. Alternatively, even if a comorbid condition is not considered as relevant to the vital prognosis, it may contra-indicate a specific therapy.

Intellectual disabilities and significant psychiatric comorbidities may also prevent the full assessment of the outcome of the trial if there are no objective measurable results available as outcome. Some of those issues can be addressed by randomisation; those studies are, however, likely to exclude several important groups of patients, such as elderly people, those with multiple comorbidities, people with intellectual disabilities or with psychiatric conditions.

Several causes of bias also exist between comorbid conditions and the studied disease. Comorbidities may result from long term exposure to the medication of the studied disease. In some conditions such as epilepsy, that are actually the symptom of an underlying cause, the underlying cause may at times be considered a comorbidity (for instance brain tumour in epilepsy), or the comorbidity may be another manifestation (with the studied disease) of the underlying process. Some comorbidity (such as in stroke) may also be a risk factor of the studied disease. Comorbid conditions may also arise from the consequence of neurological conditions (such as traumatic lesions due to falls).

We will review comorbidities of some major neurological conditions and how they can influence the treatment and outcome of the principal neurological conditions.

Comorbidities in neurological conditions

Psychiatric conditions, especially depression, are probably the most common comorbidity associated with neurological conditions. Psychiatric comorbidities are common in people with multiple sclerosis[2]. The lifetime incidence of depression in people with multiple sclerosis was reported as up to 50%, nearly three times higher than in the general population whereas the 12-month prevalence of depression was as high as 14%, twice that of the reported prevalence in the general population. The lifetime incidence of anxiety disorders in people with multiple sclerosis was also similarly increased with incidence as high as

35% in people with multiple sclerosis. Depression is also common in all stage of stroke recovery and seems not to be related to the location of the stroke [3].

Several population-based studies have shown that people with epilepsy have a higher prevalence of depression than the general population; 20-40% of people with epilepsy have major depression[4]. The prevalence of depression in people with refractory epilepsy in referral centres is probably higher than in people with epilepsy in the community. Treatment with antiepileptic drugs is a major confounder (as some medication may worsen mood disorders), but longitudinal follow-up studies show that the incidence of suicide attempts is highest shortly before the initiation of antiepileptic medication and decreases thereafter. This suggests that depression is linked with epilepsy rather its treatment.

The prevalence of depression was also shown to be increased in people with migraine compared with the general population or people with other medical conditions [5]; even after correcting for demographic, age , and other chronic health conditions, people with migraine showed a 1.6 times increased risk of developing a major depressive episode compared with the general population [6]. Depression is also a major comorbidity of Parkinson's disease; it is widely accepted that almost every second person with Parkinson's disease will develop depression during the course of their disease [7]. The symptoms may be episodic or may persist in the longer term; milder episode are very common. Cross-sectional studies in people with Parkinson's disease showed that a quarter of people have a major depressive episode. Depression in Parkinson's disease seems not to be explained by reactional factors as it does not parallel the motor course of the disease.

Further to this increased prevalence of depression in neurological disease, there is an intimate relationship between several diseases and depression. Several conditions such as epilepsy and migraine show a bidirectional association with depression [8, 9]; longitudinal studies showed that having depression increases the incidence rate of those neurological conditions and conversely that having

those neurological diseases increases the rate of depression. This bidirectional association suggests common risk factors underlying both depression and those neurological conditions. In other conditions such as in Parkinson's disease, depression was suggested to be related to discrete loss of noradrenergic and serotonergic neurons as well as degeneration of dopaminergic neurons [7], while other authors suggested that it may be the neurobiological counterpart of impulse control disorders [10].

Comorbidities in neurological conditions are not limited to psychiatric conditions; several neurological conditions have been shown to be associated with somatic comorbidities. Several community studies using either self-reported diagnoses or registers have shown a higher prevalence and incidence of somatic conditions in people with epilepsy than in the general population (figure1)[11]. This increase is not limited to specific somatic comorbidities, but affects the majority of conditions assessed in each study. This increased prevalence of somatic comorbidities is not fully explained by unfavourable socio-economic factors among people with epilepsy. People with epilepsy have greater utilization of healthcare services for comorbid conditions [12], and necessitate higher healthcare costs than the general population after excluding epilepsy-related costs [13]. Migraine with aura, for instance, was shown to have a bidirectional association [14, 15], suggesting common underlying risk factors with epilepsy.

Migraine [16] has also been shown to be associated with several somatic comorbidities. A number of studies suggested an increase prevalence and incidence of stroke in both women and men [17]. Similarly, other cardiovascular conditions, such as ischaemic heart disease (with an up to threefold increase) have been shown to be increased in people with migraine [18]. The prevalence of restless legs syndrome was found to be significantly higher in people with migraine than in people with tension or cluster headache [19]. Two studies suggested that people with migraine are at higher risk of obesity [20]. Several studies suggested an association with irritable bowel syndrome. People with migraine were also found to have

twice as many sleep problems as relatives without migraine, independent of potential psychiatric symptoms [21]. Somnambulism was also suggested as being specifically associated with migraine rather than with other types of headache. One study [22] suggested that pregnant women with migraine would be at higher risk of adverse pregnancy outcomes than matched controls, with an increase approaching threefold. People with migraine, however, do not seem to have an increased prevalence of cancer, in particular women with migraine and gynaecological cancer.

There have been some suggestions that people with multiple sclerosis also have an increased burden of concurrent somatic conditions [2]. A Dutch study using a national register [23] found an increased prevalence of liver and gallbladder disturbance and of other unclassified conditions among the 31 comorbidities assessed among people with multiple sclerosis when compared with the general population. Liver test disturbances can, however, be due to interferon treatment. The prevalence of diabetes was significantly lower than in the general population. One systematic study [24], using a provincial register validated with medical records review, found that people with multiple sclerosis were significantly more likely to have inflammatory bowel disease, irritable bowel syndrome or migraine. Another study using self-reported diagnoses found a high frequency of hypercholesterolaemia (37%), hypertension (30%), arthritis (16%), irritable bowel syndrome (13%), and chronic lung disease (13%), after correction for demographic factors; many comorbidities seemed, however, to occur at a similar frequency to the general population[2]. Findings about the prevalence of autoimmune diseases are, however, conflicting, possibly because of differences in study design [2]. In two population-based studies, people with inflammatory bowel disease had an increased risk of incidence and prevalence of demyelinating disease, suggesting an association. In several small studies, co-occurrence of rheumatoid arthritis and multiple sclerosis was higher than expected. Some studies also suggested that systemic lupus erythematosus occurs more frequently in people with multiple sclerosis than that expected in the general population. Thyroid disease was also reported as being not uncommon in people with multiple

sclerosis though the results of the different studies were conflicting. One recent study suggested that people with multiple sclerosis have an increased incidence of circulatory conditions especially within the first years after diagnosis [25]. Epilepsy was also found significantly more frequently in people with multiple sclerosis, which is in line with the potential etiological role of multiple sclerosis in epilepsy. Some studies found an increased ~~general~~ overall prevalence of comorbid conditions in Parkinson's disease, but statistical significance was not reached in many of the conditions assessed[26]. Some conditions frequently encountered in people with Parkinson's disease, such as REM sleep behaviour disorder or dementia, were suggested as sharing the same pathophysiologic mechanisms. There is some controversy about the risk of occurrence of cancer in Parkinson's disease with some studies showing a clear increase and others finding the opposite. There is also conflicting evidence on the potential association of diabetes and Parkinson's disease, while a majority of studies also shows no increase or a relatively lower prevalence of hypertension in people with Parkinson's disease. There is conflicting evidence on the prevalence of cerebrovascular and ischemic heart disease. One study suggested that people with Parkinson's disease have a significantly higher prevalence of polyneuropathy, with the neuropathy related to B12 vitamin deficiency. There was a correlation between B12 vitamin deficiency and levodopa cumulative exposure suggesting that the neuropathy might be treatment induced[27].

Effect of comorbidities on outcome and treatment of neurological conditions

There are no systematic studies on the effect of comorbidities on neurological conditions, but there are suggestions that comorbid conditions can influence the outcome of several neurological conditions. Comorbidities may also influence the treatment and response to therapy.

Comorbidities were shown to have an impact on the mortality rate of people with neurological conditions. As well as having a greater prevalence ~~incidence~~ of depression than the general population,

Commented [GB1]: Prevalence?

people with epilepsy were shown to be at higher suicide risk [28]. In Parkinson's disease, despite a high cumulative prevalence of depression the suicide risk seems not to be markedly increased, although people treated with deep brain stimulation may be at particular risk [29]. People who had a stroke are also at increased risk of suicide which seems not to be directly related to the severity of the episode, although disabilities in severe stroke may prevent the possibility of committing suicide [30]. The suicide rate is also significantly increased in people with multiple sclerosis especially in the first years after the diagnosis, though again disabilities may prevent suicide later in the course of the disease.

The burden of somatic comorbidities also leads to premature mortality in several neurological conditions. People with epilepsy have an increased mortality rate even after excluding sudden unexpected death in epilepsy (SUDEP) which is linked with seizures. People with epilepsy have a two to three fold increased mortality rate even up to 20 years after the diagnosis was established [31]. There are, however, several confounders such as the underlying cause of epilepsy and the potential long term effects of its treatment. Despite these biases, there is evidence that people with epilepsy are more likely to die prematurely due to cerebrovascular disease, even people without a stroke before epilepsy onset [32] and regardless of treatment exposure [33]. People with epilepsy are at risk of premature mortality due to cancers other than brain tumours, and due to cardio- and cerebrovascular disease [31]. The role of comorbidities in Parkinson's disease mortality is also unclear. Some studies have suggested that the role of comorbidities (diabetes, hypertension, chronic obstructive pulmonary disease, osteoarthritis, stroke, and heart disease) is negligible. Others [34] found significantly increased mortality rates due to cerebrovascular disease, respiratory disease and ischemic heart disease. It was not clear, however, whether vascular Parkinsonism could have been diagnosed as idiopathic Parkinson's disease in this community study. People with multiple sclerosis also have high mortality rates from comorbid conditions such as cardiovascular diseases [35].

In clinical practice, the choice of a particular treatment is often guided by the general medical (thus comorbidities) of the person. If a particular treatment, along with its main effect, has properties that may be beneficial to a comorbid condition, it may be preferred to a usual standard treatment option of the main disease. For instance, if a treatment has anti depressive properties, it may be preferred in a person with major depression. Conversely, a treatment may not be chosen if it has properties that may worsen a comorbid condition.

There are also suggestions that comorbidities and age can influence treatment outcome in neurological diseases and interfere with the symptoms of the disease. Age is well known as influencing the treatment of Parkinson's disease in term of cognitive side effects induced by dopaminergic agonists, similar to the anticholinergic medication used for tremor-dominant forms. Conversely younger age at Parkinson's disease onset, longer disease duration and male gender were shown to be risk factors for dopaminergic dysregulation syndrome and impulse control disorders. Substance addiction and "impulsive sensation seeking" personality traits were also shown to be risk factors. Ageing, independent from comorbid degenerative disease, was suggested as increasing the chance of remission of people with chronic epilepsy, probably by increasing the response to antiepileptic medication[36]. Obstructive sleep apnoea may worsen epilepsy, possibly due to factors such as sleep deprivation, interference in sleep consolidation and episodes of desaturation [37]. Obstructive sleep apnoea was shown to be comorbid with epilepsy in up 33% of people with drug resistant epilepsy, but higher seizure frequency has also been suggested as not being associated with obstructive sleep apnoea [37]. Trials with continuous positive airway pressure (CPAP) suggest that correcting obstructive sleep apnoea can improve epilepsy. A study [38] compared the epilepsy outcome of people with epilepsy and migraine compared with matched people with epilepsy only and found that, in the long term, people who had comorbid migraine were significantly less frequently seizure-free and were more frequently taking AED polytherapy.

Recently depression was also suggested to be associated with poor outcome in temporal lobe epilepsy surgery [39].

In multiple sclerosis, the absolute frequency of most autoimmune diseases is too low to have a substantial effect at the population level. Thyroid disease is more important because of its higher frequency and potential contribution to fatigue, a common symptom in multiple sclerosis[2]. Comorbidities may also interfere with the choice of treatment. The presence of a concomitant autoimmune condition associated with multiple sclerosis may preclude the use of natalizumab, as the use of an immunosuppressant (such as azathioprine) significantly increases the risk of developing progressive multifocal leucoencephalopathy [40]. Pre-existence of uveitis in people with multiple sclerosis was shown to increase significantly the incidence rate of fingolimod-associated macular oedema with up to 20% of people developing this complication; diabetes was also a risk factor [41]. There are also suggestions that fingolimod should be used carefully in people with cardiovascular risk factors.

In migraine, it was suggested that obesity is an aggravating factor as it was shown to be associated with chronic daily headache, whereas this was not the case in tension headache [42]; other studies found a correlation between obesity and the frequency of headaches. Others wondered whether it may be the consequence of disturbed eating behaviour due to more severe migraine, as found in experiment models [43]. The association with patent foramen ovale remains more controversial as some studies did not find any differences in its prevalence whereas others found its closure could be an effective treatment of migraine [44].

An increased burden of psychiatric and somatic comorbidities is a common problem in people with neurological disease. As well as the morbidity they induce, they increase the long term mortality rate independent of the neurological condition with which they are associated. In some situations, comorbidities or/and age also interfere with the treatment either in term of efficacy or adverse events.

The presence of comorbidities should not be underestimated. Despite heterogeneity, comorbidities should actively be taken into account when choosing a treatment and assessing its response.

Acknowledgement

The authors wish to thank Dr Myriam Schluep and Dr Christian Wider for their help in the preparation of this chapter.

References

1. Feinstein, A.R., *The pre-therapeutic classification of co-morbidity in chronic disease.* Journal of chronic diseases, 1970. **23**(7): p. 455-468.
2. Marrie, R.A. and R.I. Horwitz, *Emerging effects of comorbidities on multiple sclerosis.* The Lancet Neurology, 2010. **9**(8): p. 820-828.
3. Hackett, M.L., et al., *Frequency of Depression After Stroke: A Systematic Review of Observational Studies.* Stroke, 2005. **36**(6): p. 1330-1340.
4. Gaitatzis, A., M.R. Trimble, and J.W. Sander, *The psychiatric comorbidity of epilepsy.* Acta Neurologica Scandinavica, 2004. **110**(4): p. 207-220.
5. Molgat, C.V. and S.B. Patten, *Comorbidity of major depression and migraine--a Canadian population-based study.* Canadian journal of psychiatry. Revue canadienne de psychiatrie, 2005. **50**(13): p. 832-7.
6. Modgill, G., et al., *A Population-Based Longitudinal Community Study of Major Depression and Migraine.* Headache: The Journal of Head and Face Pain, 2012. **52**(3): p. 422-432.
7. Marsh, L., *Depression and Parkinson's Disease: Current Knowledge.* Current Neurology and Neuroscience Reports, 2013. **13**(12): p. 1-9.
8. Breslau, N., et al., *Comorbidity of migraine and depression: Investigating potential etiology and prognosis.* Neurology, 2003. **60**(8): p. 1308-1312.
9. Kanner, A.M., *Depression and epilepsy: A bidirectional relation?* Epilepsia, 2011. **52 Suppl 1**: p. 21-7.
10. Vriend, C., et al., *Depression and impulse control disorders in Parkinson's disease: two sides of the same coin?* Neuroscience and biobehavioral reviews, 2014. **38**: p. 60-71.
11. Gaitatzis, A., et al., *The Epidemiology of the Comorbidity of Epilepsy in the General Population.* Epilepsia, 2004. **45**(12): p. 1613-1622.
12. Copeland , L., et al., *Psychiatric and medical admissions observed among elderly patients with new-onset epilepsy.* BMC health services research, 2011. **11**(1): p. 84.
13. Ivanova, J.I., et al., *Economic burden of epilepsy among the privately insured in the US.* PharmacoEconomics, 2010. **28**(8): p. 675-85.
14. Ludvigsson, P., et al., *Migraine with aura is a risk factor for unprovoked seizures in children.* Annals of Neurology, 2006. **59**(1): p. 210-3.

15. Ottman, R. and R.B. Lipton, *Comorbidity of migraine and epilepsy.* Neurology, 1994. **44**(11): p. 2105-10.
16. Wang, S.J., P.K. Chen, and J.L. Fuh, *Comorbidities of migraine.* Frontiers in neurology, 2010. **1**: p. 16.
17. Stang, P.E., et al., *Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study.* Neurology, 2005. **64**(9): p. 1573-7.
18. Rose, K.M., et al., *Migraine and other headaches: associations with Rose angina and coronary heart disease.* Neurology, 2004. **63**(12): p. 2233-9.
19. Chen, P.K., et al., *Association between restless legs syndrome and migraine.* Journal of neurology, neurosurgery, and psychiatry, 2010. **81**(5): p. 524-8.
20. Peterlin, B.L., et al., *Obesity and migraine: the effect of age, gender and adipose tissue distribution.* Headache, 2010. **50**(1): p. 52-62.
21. Vgontzas, A., L. Cui, and K.R. Merikangas, *Are sleep difficulties associated with migraine attributable to anxiety and depression?* Headache, 2008. **48**(10): p. 1451-9.
22. Marozio, L., et al., *Headache and adverse pregnancy outcomes: a prospective study.* European journal of obstetrics, gynecology, and reproductive biology, 2012. **161**(2): p. 140-3.
23. Nuyen, J., et al., *Comorbidity was associated with neurologic and psychiatric diseases: A general practice-based controlled study.* Journal of clinical epidemiology, 2006. **59**(12): p. 1274-1284.
24. Marrie, R.A., et al., *The utility of administrative data for surveillance of comorbidity in multiple sclerosis: a validation study.* Neuroepidemiology, 2013. **40**(2): p. 85-92.
25. Christiansen, C.F., *Risk of vascular disease in patients with multiple sclerosis: a review.* Neurological research, 2012. **34**(8): p. 746-53.
26. Leibson, C.L., et al., *Comorbid conditions associated with Parkinson's disease: A population-based study.* Movement Disorders, 2006. **21**(4): p. 446-455.
27. Rajabally, Y.A. and J. Martey, *Neuropathy in Parkinson disease: prevalence and determinants.* Neurology, 2011. **77**(22): p. 1947-50.
28. Pugh, M.J.V., et al., *Temporal trends in new exposure to antiepileptic drug monotherapy and suicide-related behavior.* Neurology, 2013. **81**(22): p. 1900-1906.
29. Voon, V., et al., *A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease.* Brain, 2008. **131**(10): p. 2720-2728.
30. Teasdale, T.W. and A.W. Engberg, *Suicide after a stroke: a population study.* Journal of epidemiology and community health, 2001. **55**(12): p. 863-6.
31. Neligan, A., et al., *The long-term risk of premature mortality in people with epilepsy.* Brain, 2011. **134**(Pt 2): p. 388-95.
32. Trinka, E., et al., *Cause-specific mortality among patients with epilepsy: Results from a 30-year cohort study.* Epilepsia, 2013. **54**(3): p. 495-501.
33. Olesen, J.B., et al., *Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study.* Pharmacoepidemiology and drug safety, 2011. **20**(9): p. 964-71.
34. Ben-Shlomo, Y. and M.G. Marmot, *Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology?* Journal of neurology, neurosurgery, and psychiatry, 1995. **58**(3): p. 293-9.
35. Brønnum-Hansen, H., N. Koch-Henriksen, and E. Stenager, *Trends in survival and cause of death in Danish patients with multiple sclerosis.* Brain, 2004. **127**(4): p. 844-850.
36. Novy, J., et al., *The lifelong course of chronic epilepsy: the Chalfont experience.* Brain, 2013. **136**: p. 3189-3199.
37. Foldvary-Schaefer, N., et al., *Sleep apnea and epilepsy: Who's at risk?* Epilepsy & Behavior, 2012. **25**(3): p. 363-367.

38. Velioğlu, S.K., C. Boz, and M. Özmenoğlu, *The impact of migraine on epilepsy: a prospective prognosis study.* Cephalalgia : an international journal of headache, 2005. **25**(7): p. 528-535.
39. Cleary, R.A., et al., *Predictors of psychiatric and seizure outcome following temporal lobe epilepsy surgery.* Epilepsia, 2012. **53**(10): p. 1705-12.
40. Kappos, L., et al., *Natalizumab treatment for multiple sclerosis: recommendations for patient selection and monitoring.* The Lancet. Neurology, 2007. **6**(5): p. 431-41.
41. Jain, N. and M.T. Bhatti, *Fingolimod-associated macular edema: Incidence, detection, and management.* Neurology, 2012. **78**(9): p. 672-680.
42. Bigal, M.E. and R.B. Lipton, *Obesity is a risk factor for transformed migraine but not chronic tension-type headache.* Neurology, 2006. **67**(2): p. 252-257.
43. Ray, S.T. and R. Kumar, *Migraine and obesity: cause or effect?* Headache, 2010. **50**(2): p. 326-8.
44. Dowson, A., et al., *Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache.* Circulation, 2008. **117**(11): p. 1397-404.