One year changes in disability in multiple sclerosis: neurological examination compared with patient self report

E L J Hoogervorst, M J Eikelenboom, B M J Uitdehaag, C H Polman

The most common neurological outcome measure for multiple sclerosis (MS) patients is the Expanded Disability Status Scale (EDSS). Originally, Kurtzke developed this disability status scale, later revised to a more refined classification system, known as the EDSS. The EDSS is based on a neurological examination of eight functional systems usually performed by a medical doctor. While problems of standardisation, resulting in suboptimal interrater reliability, marginal sensitivity to change and bias to locomotor function have been described, the EDSS remains a useful tool for classifying disability in MS patients.

In a longstanding invalidating neurological disease like MS where cure is not yet possible, disability as perceived by the patient is an important measure and for this purpose the Guy's Neurological Disability Scale (GNDS) was recently developed. The GNDS measures disability based on patient self report, embraces the whole range of disabilities that can be developed. The GNDS measures disability based on patient self report as measured by the physician or the result of symptoms covered by the GNDS but not included in the EDSS. In addition, we measured by the physician or the result of symptoms covered by the GNDS but not included in the EDSS. In addition, we measured by the physician or the result of symptoms covered by the GNDS but not included in the EDSS. In addition, we measured by the physician or the result of symptoms covered by the GNDS but not included in the EDSS. In addition, we measured by the physician or the result of symptoms covered by the GNDS but not included in the EDSS.

METHODS

Patients

Two hundred and fifty patients with clinically definite MS underwent longitudinal examinations of EDSS and GNDS at our outpatient clinic. Patients were diagnosed as having relapsing-remitting MS (n=126), secondary progressive MS (n=60), or primary progressive MS (n=64).

Test procedures

Disability was assessed at baseline and after one year using EDSS and GNDS. Data from EDSS and GNDS were collected in the same visit, under standardised conditions by well trained physicians. The two measurements were performed in the same order, first the GNDS followed by the EDSS.

The EDSS is divided in 20 half steps ranging from 0 (normal) to 10 (death due to MS). Each subcategory of the GNDS was scored separately ranging from 0 (normal) to 5 (maximum help required). The GNDS score is the sum score of the 12 subcategories (range 0 to 60).

Analysis

Results were analysed in several ways. We studied cross sectional correlations between EDSS and GNDS sum score at baseline and follow up. Longitudinal correlations were studied between Δ EDSS and Δ GNDS sum score, Δ functional systems, and Δ GNDS subcategories, as well as between Δ functional systems and the corresponding Δ GNDS subcategories (Δ sphincter compared with Δ bladder and bowel function; Δ brain stem compared with Δ speech and swallowing; Δ pyramidal, sensory and cerebellar compared with Δ upper and lower limb function; Δ cerebral compared with Δ cognition and mood and Δ vision compared with Δ visual).

As this analysis may be confounded by the fact that the EDSS is an ordinal scale, we also studied the total number of patients showing a clinically significant change on the EDSS and GNDS, as well as the mean change in GNDS for patients with a change on the EDSS. A clinically significant change of the EDSS was defined as a change of 1.0 point or more at EDSS levels <5.0 or 0.5 point or more at EDSS levels ≥5.0. For the GNDS a change of three or more points in the sum score was considered as clinically significant. As the threshold of significance is not well defined we performed a sensitivity analysis in which we defined a significant change on the GNDS as a change of at least 2, 4, and 5 points, as well.

Statistics

Correlations were calculated using the Spearman rank correlation coefficient (r). In this study we considered p values of less than 0.01 as significant and p values of less than 0.05 as a trend only. The strength of correlation was labelled as follows: correlations <0.40 as weak to marginal; 0.40 to 0.60 as moderate; 0.60 to 0.80 as good, and >0.80 as excellent. Agreement between clinically significant EDSS and GNDS changes was calculated using linear weighted Cohen’s k.

Abbreviations: MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; GNDS, Guy's Neurological Disability Scale

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RESULTS

Table 1 summarises patient characteristics and scores on EDSS and GNDS at baseline and follow up. Mean age at baseline was 44.3 years (SD 11.0); 38% of the patients were male and 62% were female. Average time interval from baseline to follow up measurement was 13.6 months (SD 1.9). Baseline EDSS scores ranged from 0 to 9.0 and median EDSS scores at baseline and follow up were the same (4.0). The median GNDS sum score at follow up (14.0) showed a deterioration of 1.0 point compared with baseline (13.0).

Changes in GNDS occurred independent from baseline GNDS sum scores; both frequency and magnitude of the GNDS were equally distributed along the full range of baseline GNDS sum score expressed as median (interquartile range).

Table 2 Correlations between Δ GNDS subcategories and Δ EDSS and Δ GNDS for the total population

<table>
<thead>
<tr>
<th>Δ GNDS subcategories</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>0.06**</td>
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</tr>
<tr>
<td>Mood</td>
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<td>0.48**</td>
</tr>
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<td>Vision</td>
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<tr>
<td>Bowel function</td>
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</tr>
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<td>Sexual function</td>
<td>-0.01</td>
<td>0.41**</td>
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<tr>
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<td>0.34**</td>
</tr>
<tr>
<td>Others</td>
<td>-0.07</td>
<td>0.40**</td>
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** Correlation is significant (p<0.01); *correlation shows a trend (p<0.05); ns not significant. Abbreviations as for table 1.

Table 3 shows that all functional systems only changes in brain stem, sphincter, and cerebral functional systems correlated significantly with changes in GNDS sum score, while with respect to the EDSS the situation is opposite, with the exception of the visual system, which is not correlated to either overall score.

Table 4 shows that a total of 59 patients showed a clinically significant worsening on the EDSS, whereas 37 patients showed a clinically significant improvement. A clinically significant worsening or improvement of the GNDS sum score (based on the definition of a change of at least three points being significant) was observed in 86 and 52 patients, respectively. Strikingly, opposite changes in EDSS compared with GNDS sum score were observed in 20 patients (8%): in 11 patients of 37 (29.7%) in whom there was a clinically significant improvement on the EDSS there was a 3 point or more worsening in the GNDS, whereas, vice versa, in 9 patients of 59 (15.2%) in whom there was a clinically significant worsening on the EDSS there was a 3 point or more improvement on the GNDS sum score. Poor agreement (linear weighted Cohen's κ=0.12) was found between change in disability as measured by neurologist rating of neurological examination abnormalities and patient self report.

Varying the definition of significant change in GNDS to at least 2, 4, or 5 points resulted in corresponding percentages of patients with a significant worsening on the EDSS accompanied by a significant improvement on the GNDS of 22.0% (13 of 59), 10.2% (6 of 59), and 10.2% (6 of 59) respectively. Agreement between the two disability measures remained poor with respective linear weighted Cohen's κ values of 0.11, 0.13, and 0.16.

Table 1 summarises patient characteristics and scores on EDSS and GNDS for the total population.

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** Correlation is significant (p<0.01); *correlation shows a trend (p<0.05); ns not significant. Abbreviations as for table 1.

Table 3 Correlations between Δ functional systems and Δ EDSS and Δ GNDS for the total population

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<tbody>
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<td>Visual</td>
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</tr>
<tr>
<td>Brain stem</td>
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<td>0.18**</td>
</tr>
<tr>
<td>Pyramidal</td>
<td>0.22**</td>
<td>0.06**</td>
</tr>
<tr>
<td>Sensory</td>
<td>0.30**</td>
<td>0.01**</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>0.21**</td>
<td>-0.00**</td>
</tr>
<tr>
<td>Sphincter</td>
<td>0.12**</td>
<td>0.34**</td>
</tr>
<tr>
<td>Cerebral</td>
<td>0.13</td>
<td>0.26**</td>
</tr>
</tbody>
</table>

** Correlation is significant (p<0.01); *correlation shows a trend (p<0.05); ns not significant. Abbreviations as for table 1.

Table 4 Number of patients showing clinically significant changes in EDSS and GNDS sum score

<table>
<thead>
<tr>
<th>Δ GNDS of 3 points or more</th>
<th>Significant Δ EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement n=52</td>
<td>12</td>
</tr>
<tr>
<td>No change n=112</td>
<td>14</td>
</tr>
<tr>
<td>Worsening n=86</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations as for table 1.

Table 2 shows that the only statistically significant correlation between change in the different GNDS subcategories and Δ EDSS was found for lower limb function, whereas (as expected) many more GNDS subcategories were correlated with Δ GNDS. Table 3 shows that of all functional systems only changes in brain stem, sphincter, and cerebral functional systems correlated significantly with changes in GNDS sum score, while with respect to the EDSS the situation is opposite, with the exception of the visual system, which is not correlated to either overall score.

Figure 1 shows the mean GNDS change per category of EDSS change: the profile of changes clearly indicates that for EDSS worsening in the GNDS, whereas, vice versa, for patients with a significant worsening on the EDSS there is the largest worsening on the GNDS.
Assessment of the patient’s perspective of disability is important, as reflected by the increasing number of studies incorporating such measures. To our knowledge, until now, no other large study has reported on the relation between change in neurologist rating of neurological examination abnormalities as measured by the EDSS and change in patient perceived disability.

Two important pieces of information can be obtained from the data collected in this study. In the first place we show that the correlation between one year longitudinal changes in the EDSS compared with GNDS is substantially lower than the cross sectional correlation between these measures; in the second place we show that, dependent on the criterion applied for significant change in the GNDS, 10% to 22% of the patients who have a significant worsening on the EDSS show a significant improvement in perceived disability.

It is obvious from our data that despite the profile of mean GNDS sum score changes being nicely rank ordered in relation to EDSS changes (significant or not according to commonly applied criteria, fig 1), the longitudinal correlation between EDSS and GNDS is much lower than the cross sectional correlations. Although this is partially attributable to the magnitude of one year changes being considerably smaller than the range of scores at a given point in time, detailed analyses of our data also gives rise to some other explanations. Correlations between changes in functional systems and changes in GNDS subcategories are only moderate to good for those functional systems that are (mainly) based on patient self report; those functional systems that are based on neurological examination are poorly or not at all correlated with the subcategory scores based on the patient’s perception. Table 3 shows that whereas changes in the EDSS are only correlated to changes in lower limb function, changes in the GNDS are significantly correlated to a wide range of disability subcategories, including categories that theoretically could have lead to EDSS changes (bladder function and bowel function) and categories that are not at all incorporated in the EDSS (that is, fatigue).

In conclusion there seem to be three reasons for the discrepancies in the change perceived by the patient and that measured by the physician and that may differ from the patient's self report. First, the physician perception is subjective by nature and may change over time without corresponding objective changes. This may lead to response shift and thus complicate the comparison between changes in GNDS and EDSS.

In conclusion, we present longitudinal data supporting the idea that patient’s impression of change in disability may differ not just quantitatively but also qualitatively from that of an examining physician. This seems to be because there are true differences in the change perceived by the patient and that measured by the physician and to the fact that many more dimensions of disability have an impact on the GNDS than on the EDSS. Longer follow up of our cohort and additional studies in other patient groups are required to better understand this phenomenon and to determine what consequences it can have for future clinical trial design.

**Authors’ affiliations**

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Competing interests: none declared.

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**DISCUSSION**

It is well known from other studies that the EDSS is heavily biased to locomotor function, but this study adds a unique dimension based on how disability is perceived by MS patients.

Next, to compensate for the fact that our results might have been influenced by the changes in disability that occurred over a follow up period of about one year being comparatively small, we performed additional analyses on those patients who showed significant EDSS changes. For these analyses we used widely applied definitions for significant EDSS change. In many recent clinical trials in MS this definition of a significant change has been used to define significant worsening that served as primary outcome measure to determine whether disease modifying interventions were effective or not. In an attempt to obtain information on individual patients we also analysed how many patients with significant EDSS changes have corresponding or opposite changes in the GNDS of at least 2, 3, 4, or 5 points. Based on the data by Sharrack and Hughes we defined a change of at least three points to be primary for this purpose; clinically significant worsening in the physician derived EDSS was accompanied by a clinically significant increase in disability as perceived by the patient in only less than 50% of patients. Remarkably, 15% of these patients in whom a clinically significant worsening of EDSS was documented reported a significant improvement in their own subjective perception of disability compared with 30% who reported a significant worsening whereas a significant improvement in EDSS was found.

Performing these analyses for GNDS changes of at least 2, 4, and 5 points the percentages of patients showing a significant worsening on their EDSS with an associated improvement on the GNDS would have been 22%, 10%, and 10% respectively, indicating that this phenomenon is not dependent on the specific cut off of GNDS change.

In our opinion it is highly unlikely that our observations are attributable to measurement errors with respect to the EDSS: EDSS scores were obtained by a restricted number of physicians who had undergone multiple training sessions. In addition, the percentage of patients in this study showing significant worsening in EDSS score over one year (24%) is very similar to that in many other studies. Of course the patient’s perspective is subjective by nature and may change over time without corresponding objective changes. This may lead to response shift and thus complicate the comparison between changes in GNDS and EDSS.

In conclusion, we present longitudinal data supporting the idea that patient’s impression of change in disability may differ not just quantitatively but also qualitatively from that of an examining physician. This seems to be because there are true differences in the change perceived by the patient and that measured by the physician and to the fact that many more dimensions of disability have an impact on the GNDS than on the EDSS. Longer follow up of our cohort and additional studies in other patient groups are required to better understand this phenomenon and to determine what consequences it can have for future clinical trial design.
Symptoms can predict the need for computed tomography in minor head injury

A method that uses common odds ratios to predict risk of abnormality from symptoms could help doctors to provide more appropriate care for minor head injury.

Poole odds ratios from published case-control studies of patients with minor head injury (Glasgow coma scale (GCS) 15) with loss of consciousness (LOC) or post traumatic amnesia (PTA) indicated that just three symptoms predicted abnormality on computed tomography. They were vomiting (odds ratio 4.398; 95% confidence interval 2.790 to 6.932), nausea (2.125; 1.467 to 3.057), and severe headache (3.211; 2.212 to 4.584); blurred vision and dizziness were not significant. This finding enabled patients to be subgrouped as: GCS 15a very small risk (no symptoms); GCS 15b low risk (mild headache/blurred vision/dizziness); GCS 15c intermediate risk (LOC/PTA); GCS 15d high risk (severe headache/vomiting).

The authors carried out a meta-analysis of case-control or nested case-control studies to calculate common odds ratios for five symptoms and abnormality on computed tomography. They searched Medline and PubMed between January 1990 and February 2001 and hand searched several journals. They included only full papers of studies of adults or adults and children with LOC/PTA, all of whom had been examined by computed tomography, whose data allowed common odds ratios to be calculated. Just three papers, covering 3375 patients, met the study criteria.

Minor head injury has most recently been classified as GCS 15, but it still needs to be separated from other injuries within this group. Individual studies that have tried to link symptoms to abnormality on computed tomography are nearly all flawed in some way.

The naming of parts

Many deplore the journalistic trend to label well recognised conditions by acronyms, or by recently invented names—commonly to no useful purpose. Thus neurologists may not welcome yet another two names, recorded in past literature but not in general currency. Umapathi et al apply it to signify a bent spine. Camptocormia was first an illness occurring among soldiers in World Wars I and II, and was regarded as a sign of hysteria. Persistent stooping in shallow trenches, in annoyed soldiers, was corrected by the application of plaster corsets. The other reported case was that of a chauffeur who was buried in an explosion, knocked unconscious, and experienced acute respiratory distress, and subsequent mutism and camptocormia. One séance of electrical treatment corrected the improper attitude of the trunk, though he did continue to experience “a few persistent lumbar pains”.

It would be difficult to doubt the probability that psychological factors influenced these men’s recuperation. To describe these soldiers as having cataplexy, though this was the terminology used during this period, or indeed that they suffered functional back bent, is probably unfair. They may well have suffered acute traumatic spinal injury and reactive muscle spasm (and contractures). Persistent stooping in shallow trenches, in appalling conditions of deprivation and danger, may have been contributing factors weakening the tone of paraspinal muscles. However, these case reports suggest that the traumatic injury alone may be sufficient explanation for the bent spines. The management of camptocormia in the first world war was to provide biomechanical supports, such as corsets, apparently with good results. The psychological therapies of “persuasive reeducation” were additive rather than pivotal, and faradisation (and other tortures) used only “if necessary”.

The Sandler triad of low self esteem with confusion of identity, sadomasochistic behaviour towards military authorities, and impotence were, in 1947, proposed as being an essential part of camptocormia. Umapathi’s recognised causes of camptocormia and the contributing factors however implicate organicity, as indeed do the original case reports.

Reference


Infection and multiple sclerosis

The article by Hawkes1 and the editorial commentary about the role of infectious agents in multiple sclerosis (MS) examined this question from a new viewpoint based on epidemiological observations. Several infectious agents, most not sexually transmitted, were shown in MS patients in Southard’s fine collection of shell shock cases this soldier was wounded five months previously by a bullet that entered along the auxiliary border of the scapula and emerged near the spine. “He spat blood for several days... and when he got up his trunk and thighs were found to be in a state of moderate flexion upon the pelvis, the trunk being bent almost at a right angle.” He was able to bend his trunk still further forward than ‘its habitual contracted position’ and it was evident that there was contraction of the muscles of the abdominal wall and of the iliopsoas. “No motor, sensory, reflex, trophic, vasomotor, electrical, visceral or X-ray disorders could be found.” The application of plaster corsets ‘cured’ this man’s disability within six weeks.

The pollen issue of this condition as cintrage (arching), suggesting that it was not an uncommon affliction of the French soldier. Seemingly only recorded by French neurologists, Bourry and Lhermite reported two subsequent cases.1 An infantryman was thrown into the air by the bursting of a shell, rendered unconscious and recovered experiencing violent pains in the back. He remained stooped to the right. His bent back was corrected by the application of plaster corsets. The other reported case was that of a chauffeur who was buried in an explosion, knocked unconscious, and experienced acute respiratory distress, and subsequent mutism and camptocormia. One séance of electrical treatment corrected the improper attitude of the trunk, though he did continue to experience “a few persistent lumbar pains”.

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as a cause of increased CD46. Incorporation of CD46 in the viral envelope, or a possible genetic propensity in MS patients, has also been considered as causes of increased CD46. While its origin in MS is unclear, soluble CD46 might be involved in viral pathogenesis by binding the virus in the viremic phase and allowing another to attach to CD46 and spread from cell to cell. Both HHV6 and MV are infectious agents encountered in early childhood, and HHV6 can indeed become reactivated a few weeks after primary MV infection. On the other hand, because HHV6 and MV downregulate CD46 expression on the infected cell, they may diminish the effect of each other, delaying the time of infection. Therefore, they might promote increased antibody levels in young adults through delayed infection with, or reactivation of, each other. These suggest increased antibodies against these two viruses in MS may be interrelated.

The question remains whether a cause-effect relation exists between infectious organisms and MS, or whether viruses are just a consequence of the activation of the inflammatory-immune sequence or increased susceptibility of MS patients to infection. Studies of CD46 and other viral receptors seem warranted in MS.

Infection and multiple sclerosis

The paper by C H Hawkes (Is multiple sclerosis a sexually transmitted infection?) has caused predictable distress to people with multiple sclerosis (MS) and their families. Living with MS is a difficult enough experience without such sudden and avoidable alarm. The UK Multiple Sclerosis Society’s national helpline and local branches have been inundated with calls expressing anger and anxiety.

It is hard to understand the motive for publication when your own expert editorial commentator specifically referred to the paper’s “pure speculation” and “potential to cause harm”. Did the sensational nature of Dr Hawkes’s hypothesis and the virtual guarantee of extensive publicity could it receive outweigh proper consideration of its scientific merit?

There is also the worrying question of what damage may have been caused to the reputation of MS research in the UK by the lay media coverage which was attracted. The MS Society has a current forward commitment of around £12 million to nearly 70 research projects. That money is raised by voluntary donation. Anything which could discredit the quality of research here is of material concern to us.

M O’Donovan
Chief Executive, The Multiple Sclerosis Society, M S National Centre, 372 Edgware Road, London NW2 6ND, UK; modonovan@msociety.org.uk

Reference


Ed: The journal regrets any distress caused to patients with MS as a result of the widespread publicity this article received in the media. However, we wish to emphasise that the article was subject to the usual peer review process.

BOOK REVIEWS

Neurophysiology in neurosurgery. A modern intraoperative approach


This book comprises 17 chapters contributed by 24 authors. It has clearly benefited from most of the chapters being written in a more or less homogenous style and formed into seven parts mainly based on surgical procedures: motor evoked potentials/neurophysiological base; intraoperative neurophysiology (ION) of the spinal (spinal cord monitoring); ION of peripheral nerves, nerve roots and plexuses; ION of cranial nerve and brainstem; ION of supratentorial procedures; ION during stereotactic neurosurgery for movement disorders; and ION and anaesthesia management. Most of the chapters cover the background of methodology, description of the surgical procedure, and the related neurophysiological procedure, personal experience, and case reports, which gives a balanced theoretical and practical view on the topic of each chapter. One interesting annual approach taken in this book will ensure it has a wide range of readers across “neurosurgery, neurology, orthopaedic surgery, neurophysiology, anaesthesiology, interventional radiology, and biomedical engineering”.

Chronic deep brain stimulation or neuro-modulation has extended the role of clinical neurophysiology beyond its traditional diagnostic role. This new field is touched upon briefly in the part on ION during stereotactic neurosurgery. An interesting feature of this book is that it is accompanied by a CD that certainly enhances its value. Cross references are given at the end of the corresponding chapter rather than in the list of contents in the book, and at the front page of the display.

In conclusion, it is an authoritative review of intraoperative neurophysiology much weighted on the motor system for a wide range of surgical procedures. Perhaps, in its present form, those hoping for a more systematically informed discussion on intraoperative neurophysiology of the sensory system may feel slightly disappointed.

X Liu, T Z Aziz
Clinical neurophysiology of the vestibular system, 3rd edition


The first edition of Clinical neurophysiology of the vestibular system, published in 1979, had a significance beyond its content: it affirmed that neurology had a stake in the vestibular system. Here was a neurologist (Baloh) writing with an otolaryngologist (Honrubia) about physiology, endolymphograms, and above all the vestibulo-ocular reflex—the “VOR.” The VOR is no ordinary reflex; one can measure accurately both its input and its output and come up with a transfer function for gain—a new concept then for neurology. We have learnt a lot more about measurement of vestibular function and about disorders of the vestibular system since 1979. The 2nd edition, published in 1990, and now the third edition, incorporate these advances.

And what a terrific book it still is: based on concepts, packed with facts, lucidly written, and rigorously referenced. Its structure is logical, its language is clear, so that it is not only easy to search and browse but a pleasure to read from cover to cover. And it is comprehensive—no vestibular stone is left unturned.

There are four main parts, dealing in turn with: the structure and function of the vestibular system (four chapters); the clinical and laboratory evaluation of the dizzy patient (four chapters); posterior, endolymphograms; and, above all, the vestibulo-ocular reflex—the “VOR.” It is a wonderful book, written by a top-drawer specialist in neuro-oncology, Professor Chris Yeung, who is under new management. He has made it such a classic, is that although it is no one can have it all. Anyone who sees dizzy patients needs one dizzy book on the desk. This is the one I have on mine.  

G M Halmagyi

Role of proteases in the pathophysiology of neurodegenerative diseases


This volume would be an extremely useful addition to the bookshelf of anybody with an active interest in the biochemical and pathological processes that underlie some of the more common neurological diseases. In the past the role of proteolysis in these disorders has been largely neglected because it was assumed that it represented a general non-specific metabolic process. In terms of attracting research interest the field also suffered from competition concerning the naming of these enzymes and the fact that the same enzyme might have many different names. However, as the editors point out in their Preface, this is no longer the case and they have managed to bring together an impressive array of current research on the involvement of proteases in a wide variety of disorders. From what individually might have been regarded as quite disparate sources, one can now start to see common themes not least of which is the potential therapeutic value of targeting specific proteases and the development of specific inhibitors.

If, like me, you don’t have specialist knowledge of this area I would recommend going straight to the last chapter on the mammalian proteinase genes. Here you will find a clearly laid out summary of the classification and characteristics of the four main groups of proteases (serine, cysteine, aspartic, and metalloproteases). I also found the chapter on the ubiquitin/proteasome system and the normal physiological breakdown of proteins particularly informative. Having read these two chapters you will then have a wide choice of disorders and proteases to choose from. Perhaps the most widely discussed is Alzheimer’s disease, undoubtedly because of the huge advances that have been made in the understanding of the biochemical processes underlying this disease over the past 15 years. Papain-like cysteine proteinases (cathepsins), caspases, calpains, and a novel metalloendopeptidase (EC 3.4.24.15) all appear to have some role in the pathology of Alzheimer’s disease and may, therefore, be potential targets for drug development. There is also a group of Alzheimer’s disease specific proteases that affect the processing of the amyloid precursor protein (α, β, and γ secretase) and presenilin (presenilinase). Both of these proteins are central to the development of pathology and so these enzymes in particular are key targets for current drug company research.

Apart from the interest in Alzheimer’s disease, there are other chapters covering the role of matrix metalloproteinases and calpain in the demyelination of multiple sclerosis and the key role of calpain in the pathology of traumatic brain and spinal cord injury. Further chapters describe the loss of calcium homeostasis and the subsequent pathological activation of calpain, resulting in the breakdown of key structural proteins in some neuromuscular disorders. In summary, this book has something for everyone in an area of research that holds huge promise for the future in terms of developing useful therapies for treating neurodegenerative disorders.

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CORRECTIONS

The following abstract was not printed with the article by E L J Hoogervorst, M J Eikelenboom, B M J Uitdehaag, and C H Polman (One year changes in disability in multiple sclerosis: neurological examination compared with patient self report) in the April issue of JNPN (2001;74:439–42).

Objective: To characterise the relation between one year changes in neurologist rating of neurological exam abnormalities as measured by the EDSS and changes in patient perceived disability as measured by the GNDS in patients with MS.

Methods: 250 patients with MS were recruited at an outpatient clinic. Disability at baseline and one year follow up was assessed using the EDSS and GNDS. Correlations between change in EDSS, GNDS-sum score, functional systems, and GNDS subcategories were studied as well as the significance of changes in EDSS associated with changes in perceived disability.

Results: The correlation between one year changes in EDSS and GNDS was substantially lower (0.19) than cross-sectional correlations between EDSS and GNDS, either at baseline (0.62) or at follow up (0.77). Notably, changes in functional system scores that are based on neurological examination are poorly or not at all correlated with changes in disability as perceived by the patient. Analysing the impact of a significant worsening in EDSS score we found that this was associated with significant worsening, insignificant change, and significant improvement in the patients’ perceived disability in 45%, 39%, and 15% of patients, respectively.

Conclusion: Patients’ perception of change in disability differs not only quantitatively but also qualitatively from that of an examining physician. There are true differences in change as perceived by the patient and measured by the physician and changes in many dimensions of disability are relevant to the patient and have no measurable impact on the EDSS.

The authors of the short report entitled Paraneplastic ophthalmoplegia and subacute motor axonal neuropathy associated with anti-GQ1b antibodies in a patient with malignant melanoma, published in the April issue 2003 of JNPN (2003;74:507–9), were listed in the incorrect order. The author order should read as follows: L Kloos, C W Ang, W Kruit, G Stoter, and P Sillevis.