# A new overview of neurology, epilepsy and multiple sclerosis

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Author
Dominique Lannes
Associate Medical Director
SCOR Global Life

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life@scor.com

# Introduction

**In ancient times,** the Greeks thought that epileptics were "possessed" and in the Middle Ages it was believed that multiple sclerosis was caused by stress.

**By the 19th century,** several doctors who were ahead of their times took great pains to describe these diseases in detail although they still did not have the means to treat them.

**At the end of the 20th century,** new medicines and new methods of brain imaging, such as CT and then MRI scanning, were discovered.

**In 2013,** an innovative neurology is emerging which is overcoming all kinds of hurdles: genetics, biotechnology, medical imaging, neurosurgery, the pharmaceutical industry… fundamental and clinical research are uniting so that at last we can understand these diseases, treat them and hopefully soon cure them.

These advances and the consequences they have on risk underwriting now need to be known by insurers. We propose to share with you our reflections and recommendations with this updated overview of two important neurological disorders:

- Epilepsy, which affects almost 50 million people worldwide.
- Multiple sclerosis, which affects 2.5 million people worldwide and whose frequency is rising fast.

## Epilepsy

Epilepsy is a chronic neurological disease characterised by seizures resulting from abnormal and simultaneous discharges of groups of neurons in the brain.

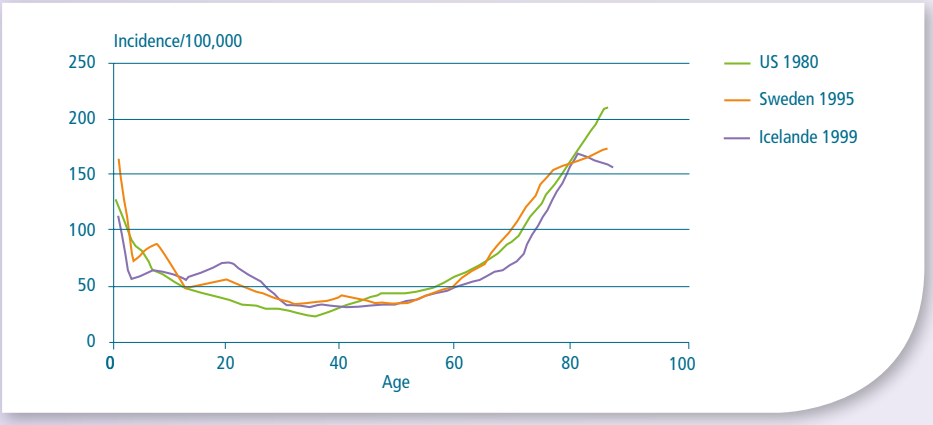
Any one can have an epileptic seizure in certain circumstances, if the brain is subject to an imbalance or aggression, such as a sudden high fever in a child or seriously abnormal states of hydration or serum electrolyte levels. However, a patient will only be considered epileptic after several seizures.

### Epidemiology

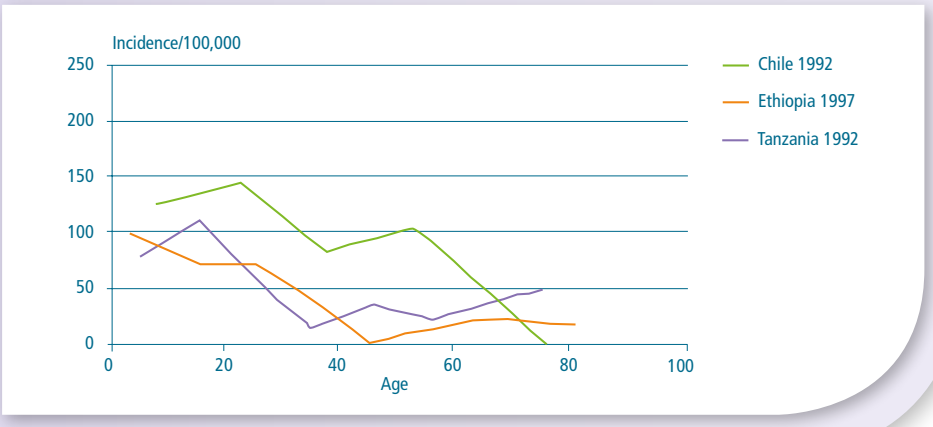
Epilepsy is a common world-wide neurological disorder. In the United States, 1.5 million people are epileptic and 10 million people suffer from the condition in Africa. In the United Kingdom 1% of the population is epileptic. Epilepsy knows no borders, geographical, social or racial. In industrialised countries, the incidence curve is quite characteristic: the incidence is low between the ages of 20 and 60, but, thereafter, the disease becomes much more common after 60. In emerging countries things are a little different: specific causes of epilepsy, parasitic and other infections, particularly affect children and young adults, and so there are far more epileptic patients aged under thirty in these countries.

**Incidence of epilepsy according to age**

**Industrialised countries**




**Emerging countries**




Source: www.ilae.org, Comprehensive Textbook, Chapter 5 – Incidence and prevalence, Poonam Nina Banerjee and W. Allen Hauser.

## Different types of epilepsy

Depending on the cause, the location in the brain and the intensity of the neuronal discharges, seizures can take very different forms from one person to another. Epilepsy can therefore present with many different clinical signs. To clarify things, it has been necessary to classify epileptic seizures.

Schematically, there are 2 forms of seizure that differ by their **clinical signs: generalised and partial seizures.** These two forms are related by their **causes: idiopathic, symptomatic** and **cryptogenic**. There are, for example, idiopathic generalised seizures and symptomatic partial seizures.

All these elements can be found in the **International League Against Epilepsy** (ILAE) *www.ilae.org/classification,* which we will detail below.

### Clinical signs

Depending on the area of the brain concerned by the neuronal discharge, the clinical signs may include sudden loss of consciousness, behavioural disorders, difficulties with speech, vision or hearing, abnormal movements and hallucinations.

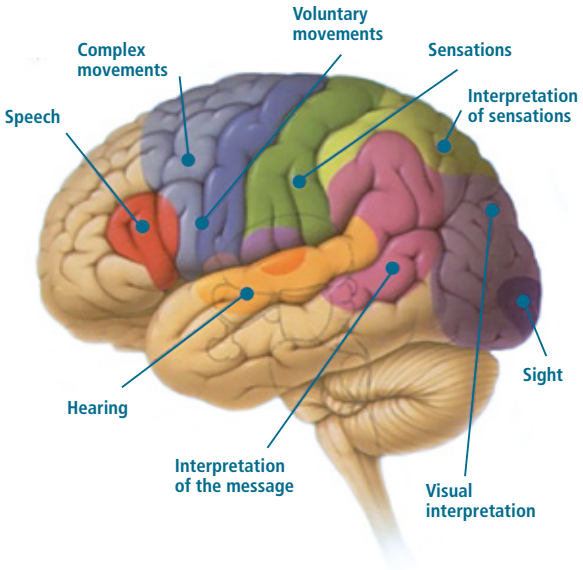
Any manifestation is possible in this field for the brain is where all our sensations, thoughts and movements originate.

- **Partial seizures,** also known as focal seizures, represent 60 or 70% of epilepsy cases. They start locally in the brain and can be of two types: simple partial seizures (no loss of consciousness), complex partial seizures (with impairment of consciousness). Partial seizures may be followed by a generalised seizure (secondary generalised seizure). The nature of the symptoms varies according to the functional area of the brain affected by the seizure.

  - Simple partial seizures are characterised by the fact that consciousness is not impaired. The associated symptoms may be: *motor symptoms* (sustained forced conjugate ocular, cephalic, truncal deviation, postural, vocal, somato-motor signs), *somatosensory or special-sensory symptoms* (visual, auditory, olfactory, gustatory, vertiginous disorders), *atonomic symptoms* (gastrointestinal, respiratory, enuretic, vasomotor and vascular), *psychic symptoms* (dysmnesic, cognitive, instinctive-affective signs, laughter, illusions, hallucinations).

**Brain topography**

The epileptic seizure can take very varied forms depending on the area of the brain concerned by the neuronal discharge.



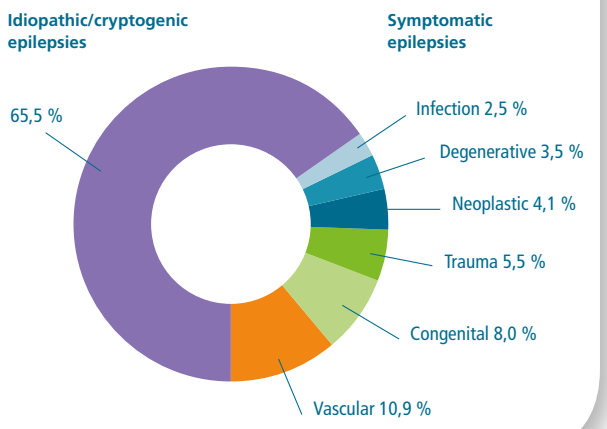

  - Complex partial seizures cause impairment of consciousness; the loss of contact with the surroundings may occur very quickly or later. These seizures may begin like a simple partial seizure and be followed by an impairment of consciousness, or consciousness may be impaired from onset. They are characterised by post-ictal amnesia and associated automatisms: *oro-alimentary* (chewing, swallowing…), *simple gestures* (hand movements, pill-rolling movements…) or *complex gestures* (buttoning and unbuttoning clothing…), *wandering, verbal automatisms* (onomatopoeia, words, phrases).

- **Generalised seizures:** the neuronal discharge simultaneously involves both cerebral hemispheres, and so the subject loses consciousness in most cases. They can be of different types: *absences* (short periods of non-receptiveness), *clonic* (spasms involving one or more muscles), tonic (sudden stiffening and contraction of the muscles), *tonic-clonic, atonic* (sudden loss of muscle tone). Consciousness may be unimpaired in myoclonic seizures (twitching and jerking of the muscles in the upper, and sometimes all four, limbs). A generalised seizure may or may not be followed by a partial seizure.

### Depending on the underlying cause:

- **Idiopathic epilepsy,** also known as "genetic epilepsy". In this case epilepsy is a direct consequence of a genetically determined abnormality of neuronal excitability and its clinical course is generally benign.
- **Symptomatic forms of epilepsy** have a clearly identified cause. This may be a tumour, a brain abnormality or a stroke, but also drug or alcohol consumption, a precise neurological disease (Huntington's disease, multiple sclerosis, Alzheimer's disease) or a high fever leading to the febrile convulsions much feared by parents.
- **Cryptogenic epilepsy** whose cause is unknown.

**Incidence of epilepsy according to aetiology**




Source: Epilepsia. 1993 May-Jun; 34(3):453-68. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Hauser WA, Annegers JF, Kurland LT.

## Contributing factors and contraindications

Patients with epilepsy can carry out all normal activities: pregnancy, breastfeeding, sport, a normal professional life are normally still possible. However, circumstances likely to trigger a seizure should be avoided: lack of sleep, drinking alcohol, fever, certain medicines that stimulate the central nervous system, hypoglycaemia or other metabolic factors, flashing lights.

Video games are a special case as only certain people are sensitive to them. With respect to sports, common sense means avoiding activities where a loss of consciousness and abnormal movements could have serious consequences (falling, losing control of a piece of apparatus, etc... examples would be mountain climbing and underwater diving).

Some patients have very specific triggers: unexpected noises, reading, strong emotions, prolonged intellectual concentration, etc.

In a work setting, each individual situation must be carefully assessed. Computer use, contrary to popular belief, is not contraindicated in epileptic patients, except if they have a proven sensitivity to screens, which is extremely rare with flat screens. Epilepsy should not therefore be a contraindication for using computers at work.

**In all cases, it is essential to keep taking all prescribed antiepileptic drugs.**

## Diagnosis, EEG and MRI

The diagnosis of epilepsy is based above all on the clinical description of the seizures. Going over the "film" of the seizure with the patient can very often point the diagnosis in a clear direction.
The medical reasoning to be followed when faced with a seizure is always:

- Is this a really an epileptic seizure?
- What type of seizure: partial or generalised?
- Is there a cause? If yes, can it be cured?
- Is the seizure an integral part of a specific neurological disease?

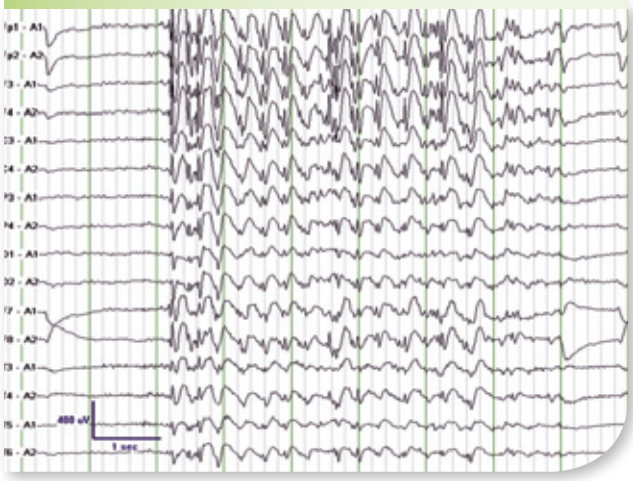
### The electroencephalogram (EEG)

EEG is a method of exploring the brain which records the electrical activity in the brain using electrodes placed on the scalp. EEG is a painless, non-invasive examination, which is used to diagnose but also to monitor epileptic patients. When

an EEG is coupled with a video recording of the seizure, the correlation between the electrical activity in the brain and the clinical signs is particularly informative and interesting.

*In the insurance context, an applicant treated for epilepsy, whose EEG between seizures is normal, can be considered as having a better prognosis in the assessment of the overall risk •*

**EEG tracing**



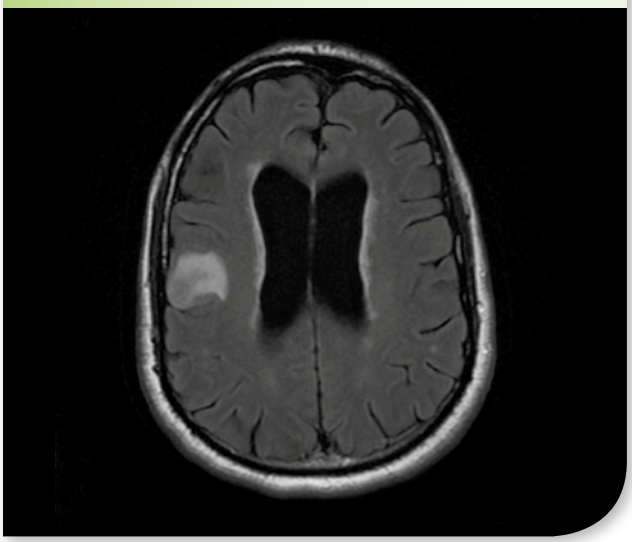
Source: B. Guéguen, CHSA

### The Magnetic Resonance Imaging (MRI)

MRI is a non-invasive method of medical imaging without ionising radiation, which can be used to examine the brain in detail "from every angle". The value of the examination lies mainly in the detection of symptomatic epilepsy, that is to say where there is a clearly identifiable cause in the brain: a brain tumour, a malformation of the brain, etc.

In difficult cases, metabolic imaging, of brain function, is necessary and this can be done by a PET Scan,. This method can, for example, reveal localised brain hypometabolism, and possibly the need for surgery.

**Brain MRI with brain tumour**



Source: Imaging centre, IMFM Paris

*It should also be noted that EEG and MRI are both non-invasive examinations and are performed systematically in patients with epilepsy in most countries. When considering a life insurance application, the contribution of these two investigations should not be neglected •*

## Epilepsy treatments

### Old medications and some more recent ones

The first drug used to treat epilepsy was phenytoin, discovered in 1937. After that came carbamazepine in 1960 and valproate in 1963. From 1990 onwards the latest generation of anti-epileptic drugs, with fewer side effects and usually greater efficacy, was introduced. They have the particularity of being broad-spectrum and can be used in both partial and generalised epilepsy.

**Anti-epileptic drugs**

| | International non-proprietary name |
|---|---|
| Classic anti-epileptic drugs | phenobarbital, ethosuximide, sodium valproate, phenytoin, carbamazepine |
| New anti-epileptic drugs | vigabatrin, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam, pregabalin |

Carbamazepine is often indicated as a first-line therapy for partial seizures and valproate for generalised seizures. If these therapies fail, a new generation anti-epileptic drug will be offered: lamotrigine, topiramate or levetiracetam. If these also fail to work, combination therapy will then be recommended: using two drugs with different modes of action.

Overall, anti-epileptic treatments keep patients seizure-free in 7 cases out of 10. If all medical treatment fails, the epilepsy is said to be pharmacoresistant and surgery must be considered. Furthermore, it must be offered without delay for certain causes of epilepsy, such as hippocampal sclerosis, for example.

*The insurer should consider the new anti-epileptic drugs as a definite improvement as they are able to stabilise many patients and they are better tolerated. However, they do not cure all types of epilepsy •*

### Surgery

When seizures are frequent and serious enough to significantly affect the patient's life and medication is ineffective, surgery may be envisaged to remove the area of the brain where the "epileptic or seizure focus" is located. The seizure focus must be located in an area of the brain where ablation will not lead to disabling neurological and neuropsychological deficits. This surgery is delicate and must be performed by a highly specialised surgeon. The techniques commonly proposed include hippocampectomy (inside of the temporal lobe), but also more complex operations involving localised resection such as lobectomy, cortectomy, hemispherectomy, corpus callosotomy and multiple subpial transection.

Other techniques such as vagus nerve stimulation and deep brain stimulation may be proposed in very specific cases. Surgery can cure epilepsy, but paradoxically and in a way that is not fully understood, it can lead to psychiatric compensation which in some cases may require hospital treatment.

*In the insurance context, caution is necessary for a few months… even after surgical treatment has halted the seizures. A patient will only be considered "cured" after a seizure free period of 1 to 2 years •*

## Comorbidities, prognostic factors and general course of the disease

Different disabilities are associated with epilepsy: a lower IQ score, attention deficit and memory impairment, slow thinking, language disorders, various psychological disorders. Mood disorders are also common in epileptics. About 30% suffer from depression. It should be noted, however, that when the epilepsy is stabilised by treatment, the incidence is low, of the order of 5%. Suicide, which is observed mainly young patients, is three times more common than in the general population.

Sudden unexplained death accounts for 8.8% of deaths of epileptic patients under 40. Generally, excess mortality is 2 to 3 times higher in epileptics, and up to 5 times higher in cases of pharmacoresistant epilepsy.

Certain criteria can identify the epileptic patients at the greatest risk:

- The epilepsy is pharmacoresistant or requires polytherapy.
- The EEG between 2 seizures is abnormal.
- There is an associated psychomotor disability.
- Early onset childhood epilepsy which is still active in adulthood.
- Seizure frequency is high (from 4 or 5 seizures a year).
- The epilepsy is symptomatic, but the cause is incurable.
- The epilepsy is of the disabling generalised myoclonic type.

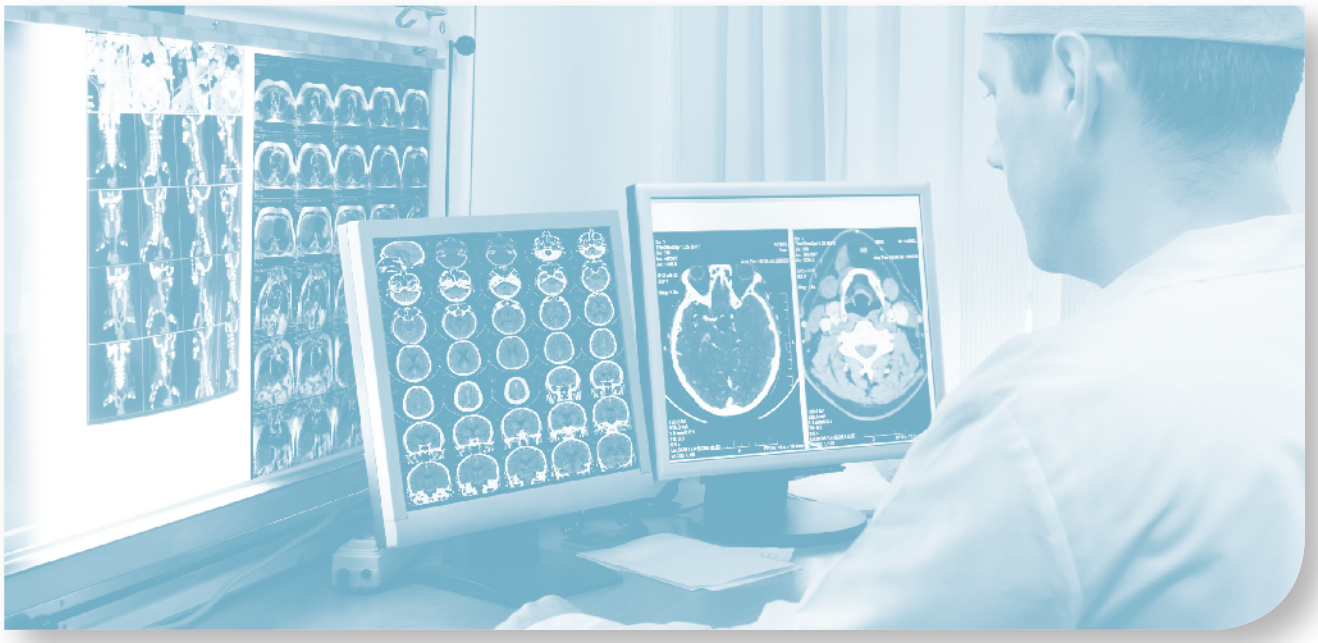
Statistically, after 20 years, the general course of epilepsy can be summarised as follows:

- 50% of patients no longer have any seizures, without any treatment.
- 20% of patients are in remission, with treatment.
- The other 30%, however, still have seizures.
- Epilepsy tends to stabilise with age.

## Employment difficulties

Epileptic seizures can occur suddenly and unexpectedly when the patient is at work, which may impact on his or her employability. This will depend on the type of seizure, their frequency and of course the job itself.
Around 20% of epileptic patients have employment difficulties, young sufferers in particular, and these occur at different levels: recruitment and keeping a job, career progression, frequent job changes, working in underqualified jobs, early retirement. The unemployment rate is 40 to 50% higher than that of the general population.
The severity of the epilepsy and inadequate or inappropriate treatment partly explain such employment difficulties, but other factors have a greater impact: a lack of professional qualifications, stigma of epilepsy in the professional environment, associated intellectual, psychiatric or motor disabilities, psychological disorders such as a lack of self-confidence or poor self-image.

*All these data and figures must be integrated by the insurer when assessing the risk relating to epilepsy*



## Assessing the risk and rating epilepsy

Underwriting an epileptic applicant can seem complex. As we have seen, the causes are multiple, the prognosis may be good or dreadful and there are a large number of clinical forms and possible courses of the disease. Accidental death and sudden unexplained death will be the major risks to be assessed in this context.

Furthermore, we have also seen how this condition related to psychosocial factors, in particular depression and social and socio-professional difficulties. These parameters must be taken into account when assessing for disability and incapacity cover.

To be able to assess an epileptic patient's application in full knowledge of the facts, it is preferable to obtain a medical certificate with the following information:

- **The cause** of the epilepsy: it is clear that epilepsy due to a brain tumour, alcoholism or which is linked to a progressive neurological disorder will not have the same prognosis as idiopathic epilepsy that has been stable since childhood, for example.
- **Annual number of seizures:** the prognosis for epilepsy with a seizure a week is different to that for epilepsy with a seizure every two years.
- **Date of the last seizure:** the more time has passed since the last seizure, the better the overall prognosis.
- **Type of seizure:** partial seizures, regardless of their cause, have a lower accident and incapacity risk than generalised seizures with a total loss of consciousness.
- **Psychosocial situation:** associated depression, invalidity, repeated sick leave, etc. are criteria that must be taken into account when assessing the risk.

In support of the clinical information, the results of the latest **EEGs** and **brain MRI scans** can also provide objective evidence on the cause of the epilepsy and on its outcome with treatment. We would stress that a recent normal EEG suggests a favourable prognosis.

To sum up, epilepsy that is well controlled by treatment, without seizures for several years and with no significant neurological cause (brain tumour, etc.) will much have a better prognosis with an extramortality ratio of less than 100% in certain cases.

Epilepsy whose cause has been cured by surgery may be considered a standard risk after an adequate follow-up period.

Conversely, symptomatic epilepsy caused by tumour, stroke or a progressive neurological disease would normally be declined.

Depending on the cause, the annual number of seizures and the time since the last seizure most cases will be taken into account and usually given from + 50 to + 200% extramortality ratings.

Caution should be exercised when considering disability and incapacity riders. Cases of perfectly stabilized epilepsy with no seizures for several years should be accepted.

## Multiple sclerosis

Multiple sclerosis (MS) is a relapsing-remitting neurodegenerative disease, characterised by inflammatory lesions of the white matter in the brain and the spinal cord.

### Epidemiology

The prevalence of MS is not uniform around the world and in fact there is a North-South gradient, that is to say the frequency of the disease diminishes as we approach the Equator.

The areas of high prevalence of the disease (around 100 per 100,000) are Northern Europe, Canada and the northern United States, while the areas of low prevalence (less than 5 per 100,000) are situated around the Mediterranean and Mexico.

There are three times more female MS sufferers than men and the average age of onset of the disease is usually about thirty. As for other autoimmune diseases, incidence and prevalence are rising fast on all continents: more than 20% over a period of about twenty years.

## Causes, contributing factors

The cause of MS is still not known. It is probably the result of an interaction between a genetic predisposition and one or more environmental factors.

Vitamin D is a powerful immune regulator: vitamin D deficiency is one of the risk factors for the occurrence of a first attack of MS. Obesity and smoking also partly explain the increase in the number of cases, in both developed and emerging countries. Finally, viral causes are also being suggested, in particular Epstein-Barr virus infection.

## Clinical signs

These will depend above all on the location of the MS lesions in the brain: depending on the area of the brain affected, the symptoms will be very different from one person to the next.

- 25% of sufferers begin their MS with visual symptoms due to optic neuritis. This often means visual disorders such as poor contrast or a difficulty in fixing objects. There may be monocular or bilateral blindness or a decline in visual acuity.
- 30 to 40% of sufferers begin their MS with paralysis or problems with their balance. They are likely to cause difficulties in walking to varying degrees.
- In some cases, pain, spasticity and spasms, genito-sphincter and erectile dysfunctions may also affect patients.

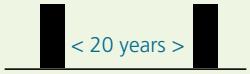
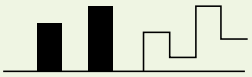
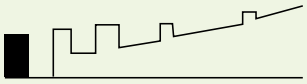
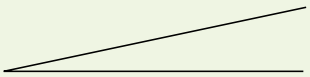
In addition to the neurological signs, about a half of patients with MS also have other disturbing disorders that are disabling in patients' daily lives: chronic fatigue, impairment of attention, concentration and memory, serious intellectual fatigability, learning difficulties.

Patients also suffer from anxiety, altered personality and often depression. These psychological abnormalities are correlated with **a suicide risk 3 to 7 times higher than that of the general population.** The cognitive and neuropsychological difficulties are independent of the severity of MS itself.

## The different progressive forms

The disease can take different forms and today there is no reliable marker to indicate how the disease will progress in an individual patient. The unpredictability concerning the progression of MS remains in 2013.
Basically MS is classified into four types, characterised by the disease's progression:

### The different progressive forms

| Form | Percentage of patients | Characteristics |
|---|---|---|
| Benign form   | 15 - 20% | EDSS score below 3 after 20 years with the disease |
| Relapsing-remitting form  | About 40% | Without sequelae after the first attacks, in spite of persistent lesions. Periods between relapses vary greatly in length: a month, a year, ten years, thirty years… |
| Secondary progressive form (SPMS)  | About 30% | The patient's symptoms worsen over the years, after a period of remission and in spite of the virtual absence of any relapses |
| Primary progressive form  | 10 - 15% | No attacks; progression of the motor, sensory and cognitive symptoms from the outset… The most serious form |

## Diagnosis, MRI

Diagnosis rests on observation of a number of clinical and paraclinical factors and progression. Three elements are important when diagnosing MS:

- The time dimension: the disease progresses with attacks occurring after varying lapses of time.
- The space dimension: there are several lesions, or demyelinating plaques in the brain or spinal cord.
- The elimination of other possible diagnoses: Before reaching a diagnosis of MS, it is necessary to rule out other neurological conditions that also progress with successive attacks.

When the diagnosis is uncertain, a lumbar puncture can be done to analyse the cerebrospinal fluid. 85 to 90% of patients have oligoclonal bands: these are a sort of signature indicating immune dysfunction.

### Diagnosis: the McDonald Criteria

William McDonald gave his name to a set of diagnostic criteria for the disease, drawn up in 2001 and revised in 2005 and then again in 2010. They constitute a balance between sensitivity and specificity and enable a reliable diagnosis of the disease. The application of these criteria makes early diagnosis possible from the first attack and takes into account the possible differential diagnoses.

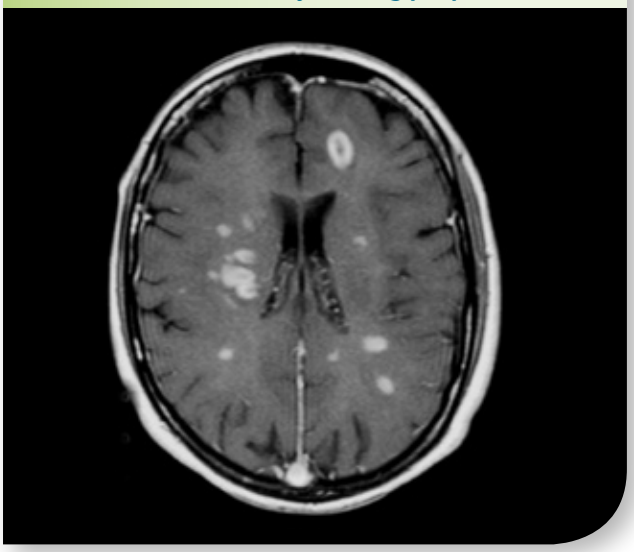
The principle behind the criteria is to establish the objective dissemination of MS lesions in the cerebral space (lesions in different places in the central nervous system), but also in time (lesions of different ages), by using clinical data, the results of the lumbar puncture and above all the patient's MRI scan. These criteria have become the reference all over the world and are used whenever a diagnosis of this condition is a possibility.

### MRI

MRI has transformed the management of the disease by detecting demyelinating plaques in the central nervous system with great accuracy. These appear in the form of "hypersignal" lesions in the brain, the spinal cord and the optic nerves. An MRI scan can also show areas of brain atrophy corresponding to areas where nerve tissue has been destroyed. In some cases, it is possible to make a diagnosis of MS just with an MRI scan, when it shows several characteristic lesions of different ages.

MRI allows the extent of the MS lesions to be objectively quantified by calculating a score known as the "lesion load". The stability of the lesion load over time is certainly a favourable factor in the assessment of the disease. In 2013 MRI is an indispensable diagnostic, monitoring and prognostic tool in daily medical practice. MRI's contribution will be even greater when it is performed with homogeneously validated protocols in all radiology centres.

**Brain MRI scan with demyelinating plaques**

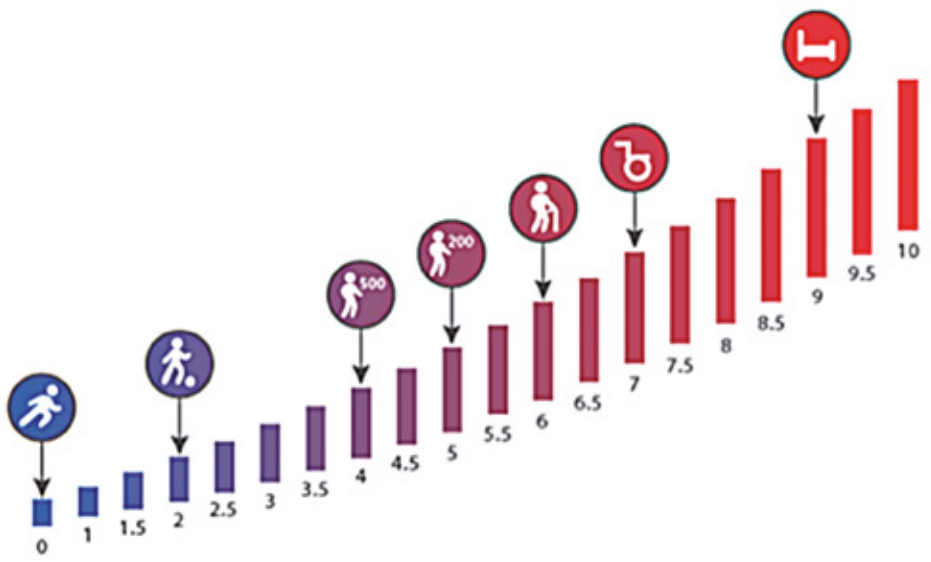


Source: CHU Lille

## Measuring disability, the EDSS scale

MS is the leading non-traumatic cause of severe acquired disability in young people. The impact of the incapacity and disability on daily family and working life is often considerable. All over the world this disability is measured using the EDSS (Expanded Disability Status Scale), which ranges from 0 to 10.

**EDSS (Expanded Disability Status Scale)**

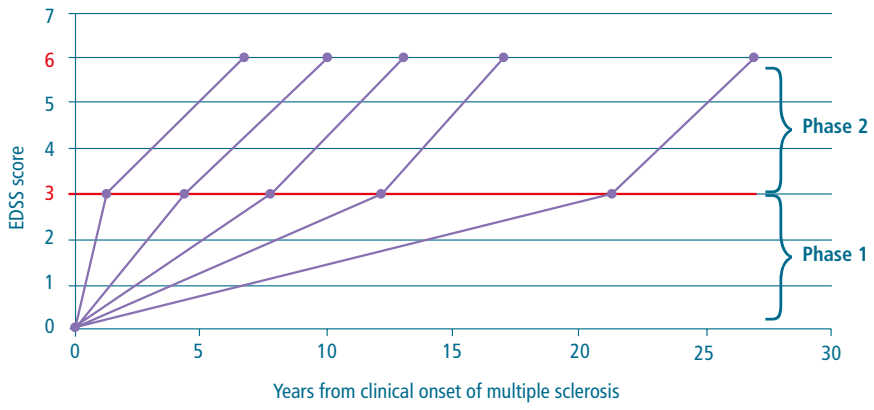



0: normal neurological examination
2: one functional system is affected: for example a sensory disorder or an isolated motor deficiency
4: patient is still able to work, but has limited walking ability
5: patient no longer able to walk more than 200 metres unaided
6: unilateral assistance required to walk 100 metres
7: essentially restricted to a wheelchair.
9: bedridden patient

Source: Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale. Neurology 1983; 33: 1444-1452

The variability of the progression of MS is very high up to an EDSS score of 3, which means that in these cases the disease is totally unpredictable. It may take a few months to reach an EDSS score of 3… or 20 years. This score may never be reached in certain benign forms. On the other hand, once the EDSS score is over 3, the progression becomes more homogeneous. All sufferers take an average of 6 to 7 years to reach a score of 6. The aim of the treatments is therefore to prevent patients getting past a score of 3-4, because after that the therapeutic possibilities are more limited.

**Progression of disability in MS**




Disability progression during phase 2 (mean time from DSS 3 to DSS 6) in five subgroups defined according to the duration of phase 1 (mean time from multiple sclerosis clinical onset to DSS 3) in the 718 multiple sclerosis patients who had reached both DSS 3 and DSS 6.

Source: Brain a Journal of Neurology, Brain 2010: 133; 1900–1913, Evidence for a two-stage disability progression in multiple sclerosis - Emmanuelle Leray, Jacqueline Yaouanq, Emmanuelle Le Page, Marc Coustans, David Laplaud, Joël Oger and Gilles Edan.

*In the insurance context, the EDSS score is the pivotal element of underwriting •*

## Treatments and the multidisciplinary approach

Although there has been no revolution, there have been undisputed advances in the treatment of MS over the last fifteen or so years. Progress has been made in treating the symptoms and improving the quality of life for patients, although much remains to be accomplished.

### Disease-modifying drug treatments

These drugs aim to reduce the frequency of the attacks and slow the progression of the disease. It is important to act as early as possible on the inflammation, which destroys the myelin and then the neurons and leads to the progressive form of the disease. In 2013, disease-modifying drug treatments are usually prescribed from the first attack.

- **In the relapsing-remitting forms, immune modulators,** which appeared between 1993 and 2000 (beta interferons and glatiramer acetate), can be used to treat 50% of sufferers. They are non-toxic.
  After 5 to 10 years, two thirds of patients no longer respond to these treatments and it then becomes necessary to prescribe **immune suppressants,** drugs which came onto the market between 2001 and 2011.
  These treatments reduce the relapse rate by 54% for fingolimod and 68% for natalizumab; they are therefore more effective, but they have adverse effects that render the risk/benefit ratio debatable in some patients.
  A third line of treatment is sometimes envisaged, with molecules such as cyclophosphamide and mitoxantrone. Exceptionally, autologous bone marrow transplants are performed.

- I**n the secondary progressive forms of MS** the impact of treatments is very modest.
- **In the primary progressive forms** no treatment has been found to have a clear significant impact.

### A therapeutic revolution in the near future?

The treatment of the relapsing-remitting forms of MS could see a major advance if current clinical trials live up to their promises. Three new treatments are expected in 2014. One is an immune suppressant (BG12), one an immune modulator (teriflunomide) and one a monoclonal antibody that binds to and kills lymphocytes (alemtuzumab). Other experimental molecules are also being tested, including laquinimod, ocrelizumab, daclizumab.

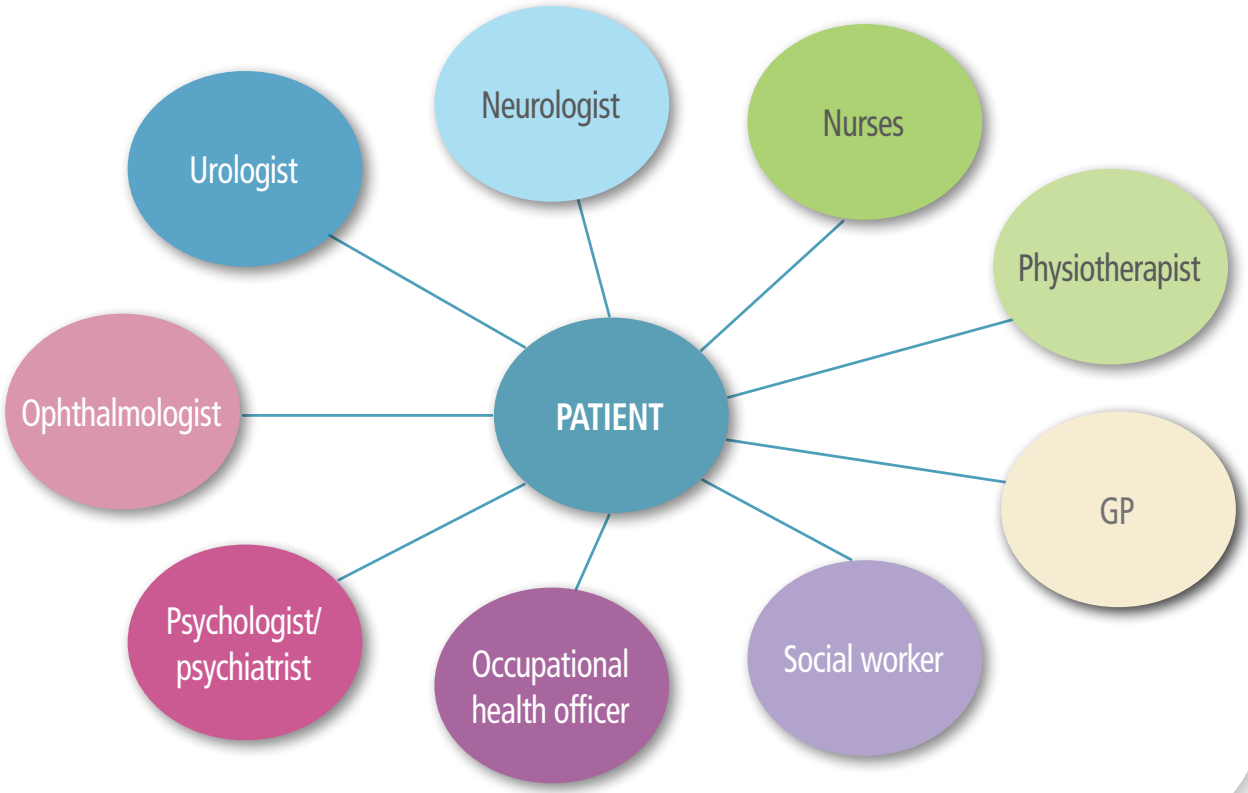
In the primary progressive forms, trials are underway on new therapies, but the results are not expected before 2020!

### Multidisciplinary approach

MS is a chronic disease in young adults that does not require any particular precautions on a day-to-day basis apart from a few lifestyle changes compared to life "before the disease".

In the advanced forms, the severity of the disease in terms of disability requires support and a multidisciplinary approach, especially in the progressive forms where treatments are relatively ineffective. It is in this area that the most progress has been made.

**Multidisciplinary approach (G-SEP)**



## Prognostic factors

There is a high level of uncertainty about the progression of the disease. To establish a functional prognosis, it is important to know how the disease began: the history of the first five years is essential in estimating the subsequent risk. The second important factor is the analysis of the very first MRI scan.

Studies of large populations of patients have shown that for equivalent periods of illness, there are **favourable and unfavourable factors** in the prognosis.

| Favourable | Unfavourable |
|---|---|
| • Early onset (young) | • Late onset (> 40 years) |
| • Initials signs: *optic neuritis, paraesthesia* | • Initials signs: *motor, cerebellar or multifocal signs* |
| • Few attacks (first 2 years) | • Progressive form |
| • Long time to reach EDSS 3 | • Numerous attacks |
| • Subnormal MRI | • Short time to reach EDSS 3 |
| | • Very abnormal MRI |

The patient enters a secondary progressive phase of the disease on average 10 to 15 years after the onset of MS, or statistically between the ages of 40 and 45, but, as always with this condition, with an extreme degree of variability from one individual to another.

15 years after the onset of the disease, approximately one patient in two will need a walking stick to walk 100 or 200 metres. Similarly, it takes an average of 25 years to reach the stage where a wheelchair is necessary. Modern therapies for MS are tending to extend these timeframes.

Three other prognostic factors have currently been identified. These are:

- Smoking and obesity, which aggravate the disease.
- Gender: men often have more severe forms than women.

Source: Confavreux C, et al. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003; 126:770-82. Brex PA et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002; 346(3):158-64.

## Risk assessment and rating of multiple sclerosis

MS is a neurodegenerative disorder that reduces life expectancy on average by 5 to 10 years, due to a small percentage of very severe forms.
The difficulty for underwriters resides in the extreme variability and unpredictability of the disease: the number of attacks, whether it is relapsing-remitting or progressive, the location and number of the demyelinating plaques in the central nervous system, which have multiple and varied consequences, etc. Nevertheless, the insurer needs to have quite a clear and objective idea of the possible future progression of the disease in an applicant.

In order to assess the application of a patient suffering from MS as well as possible, it is preferable to obtain a medical certificate including the following information:

- **The history of the disease** with the date of the last attack and of course the type, relapsing-remitting or progressive.
- **The applicant's level of disability** with the EDSS score, which is an objective element indispensable to rating.
- **The latest MRI report** with the lesion load, if this has been done.

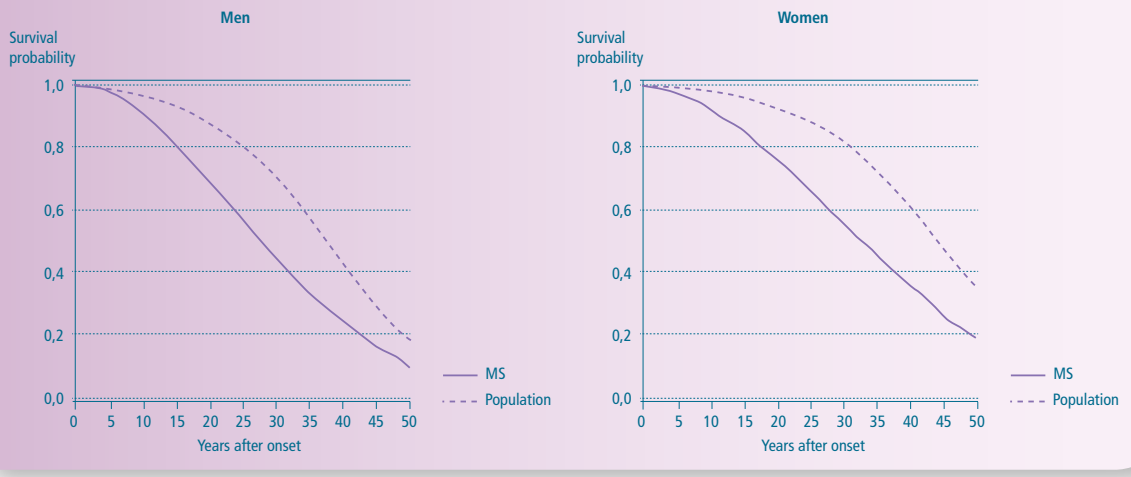
**The progressive forms of MS are not insurable unless they are being treated, whatever the type of insurance.**

Relapsing-remitting forms must be analysed taking into account:

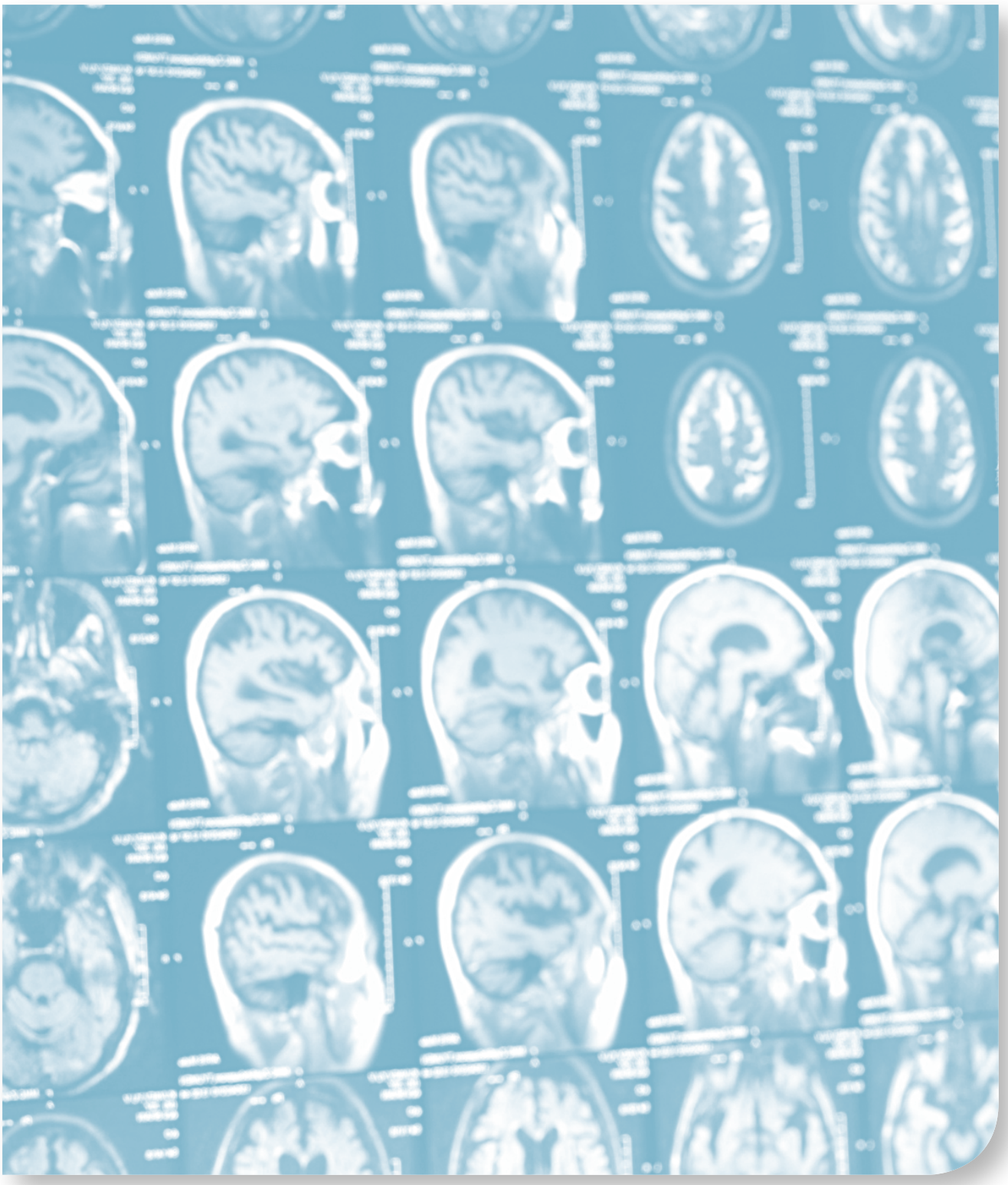
- The EDSS score, which must be < 6.
- The number of attacks and especially the length of time since the last attack. Clearly not having had an attack in the last 5 years is more favourable than having had one 6 months ago.
- Depending on these different parameters a rating of 25 to 200% will be proposed for death cover.
- The rating will be modulated favourably if the lesions are stable in 2 MRI scans at least two years apart.

With respect to disability cover, MS is an unpredictable condition, often disabling and associated with intense fatigue and depression: in this area, caution is therefore still recommended in 2013.

Survival of Danish patients with MS compared with the general population (actuarial method)




Source: Oxford Journals, Medicine Brain, Volume 127, Issue 4, Pp. 844-850. Henrik Brønnum-Hansen , Nils Koch-Henriksen and Egon Stenager.



# Conclusion

This update on epilepsy and multiple sclerosis is intended to help underwriters to understand the general picture, the latest developments and the main issues concerning these two chronic neurological conditions. Although progress has unquestionably been made in diagnosis and therapies, this can by no means be considered a revolution. Our assessment of the risk has, however, become more refined and we are able to rate the real risks more accurately.

In the insurance context, the information needed for these two conditions, which both feature intermittent attacks, will always include:

- The number of seizures or attacks per year.
- The length of time since the last seizure or attack.
- Knowledge of the patient's neurological, but also neuropsychological condition, in particular the depression and asthenia often associated.
- The information provided by MRI: the MRI report must be part of the medical file provided by the applicant in most cases.

**The coming years promise to be rich in discoveries in the neurological field.**

SCOR Global Life
5, avenue Kléber
75795 Paris Cedex 16
France
www.scor.com

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