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LETTER FROM THE EDITOR

Dear Reader:

In this issue we present articles concerning diseases of the nervous system. In addition, we introduce a new contributor, Richard Rougeau, M.D., who recently joined the medical team at RGA.

The human nervous system is a complex organ, with its own unique set of signs and symptoms when it fails to properly function. Diseases of the central nervous system are particularly difficult to assess due to the physical barriers that prevent easy examination. As such, there is a tendency to remain unaware of nervous system disease until relatively late in the process. In this issue we will examine some of the diseases that affect the nervous system, and in particular the central nervous system.

Jeanne Mariani, an underwriter at RGA, will provide an overview of seizure disorders. Dr. Rougeau will provide insight into the underwriting of people with Parkinsonism. Robert Profumo, M.D., has written an article dealing with the prognostic factors that can allow us to stratify risk in people suffering from multiple sclerosis. Lastly, I discuss tumors of the central nervous system, using meningiomas and astrocytomas as examples.

I hope you find these articles informative. As always if you have any comments, questions or suggestions for further articles, please send them to us. References for the articles in this issue are available on request.

Sincerely,

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PARKINSONISM

Parkinsonism is a syndrome characterized by tremor at rest, rigidity, bradykinesia/hypokinesia, flexed posture of neck, trunk and limbs, and loss of postural righting reflexes. It can be induced by drugs, (eg. phenothiazines), infection (postencephalitic/AIDS), toxic metabolic states (eg. manganese poisoning), repeated head trauma, etc. In fact, however, the most common presentation is idiopathic (Parkinson's Disease) which is believed to result from a complex interplay of various genetic and environmental factors. The primary brain lesion that results consists of a degenerative process in the substantia nigra, which causes a relative loss of dopamine as a neurotransmitter. It is estimated that 60-85% of nigral neurons and striatal dopamine are lost prior to the development of Parkinson's Disease (PD) symptoms.

It is difficult to generalize regarding the natural history of Parkinsonism, largely due to the fact that the true prevalence is unknown. Estimates range from 107-187 per 100,000 population in Europe and North >>>

>>>America. It tends to be underdiagnosed, usually because of the insidious nature of its onset and chronic irreversible progression. In many cases patients and their care providers may incorrectly attribute symptoms and signs of the disease to the "normal" aging process. Consequently, vital-statistics data tends to underreport the relative contribution of PD to overall mortality. Cause of death is usually attributed to comorbid illnesses (CAD, pneumonia, cancer, cerebrovascular disease, urosepsis), however, estimates of survival are approximately nine-to-ten years from the onset of symptoms with wide variability among individual subjects. The mean age of clinical onset of PD is the mid-50s, but the range is very wide and some patients present as young as their mid-20s. Young patients tend to present with tremor predominant disease and elderly patients with gait dysfunction.

The greatest therapeutic benefits from treating Parkinsonism have largely arisen from the use of Levodopa (Dopan/Laradopa) as 80% of patients tend to respond favorably. Many draw benefit from the use of Levodopa for in excess of five years. It is generally accepted that those who respond best increase their longevity by several years, but this has not been quantified to any extent. The prolonged use of this medication, however, is often associated with development of two motor problems namely, fluctuations and dyskinesias in about 50% of patients within five years of treatment. Fluctuations are irregular and clinically unpredictable responses to medications; dyskinesias are involuntary purposeless spasmodic movements associated with abnormal muscle tone. Also occurring are psychiatric reactions such as confusion, hallucinations and delusions. There does, however, seem to be evidence of increased survival in those patients who can remain on therapy for more than two years.

In a recent large multi centre study in Australia, the standardized mortality ratio (SMR) for all patients with PD was 1.58 ($p < 0.001$). There were no significant differences between the sexes. The mean duration of disease until death was 9.1 years. The most common cause of death was pneumonia. Older age of onset correlated with increased risk of death, but the SMR was increased even in those younger than 70. Early use of bromocriptine did not reduce mortality or slow disease progression.

COMMENT: Although this study of 149 individuals did not age stratify the study participants, it is reasonable to assume that the SMR reflects the experience of an elderly cohort and should not be viewed as representative of that which occurs in younger patients. The applicable

mortality ratios in younger patients await further study. With respect to the frequency of dementia in PD, prevalence studies have shown approximately one quarter of patients had dementia (range 20-33%). Dementia was associated with depression, institutionalization, older age at onset (> 70 years), greater severity of neurologic symptoms, being confused or psychotic on Levodopa or having facial masking as a presenting sign. The relative risk for the development of dementia with PD (after adjusting for age, education, and gender) is almost twice that of community dwelling control subjects.

Susceptibility to PD is increased in first-degree relatives of both sporadic and familial cases. The pattern of inheritance and the relationship between genetic and environmental risk factors await further study.

Recent advances in the treatment of PD have made for significant improvement in quality of life and for somewhat more modest increases in survival. Prior to the advent of Levodopa, mortality among PD patients was three times the normally expected mortality. It remains the most effective drug for PD but long-term use is complicated by serious limiting side effects. Selegiline, amantadine, and anticholinergics are still used but must be employed with caution especially in the elderly. Catechol-o-methyltransferase (COMT) inhibitors too are useful adjuncts to Levodopa therapy but are associated with adverse effects as well. Surgical treatment includes globus pallidus internal-segment pallidotomy, deep brain stimulation and fetal nigral cell transplantation. Future developments in these rapidly advancing areas include elucidation of the mechanisms of action of electrical stimulation and technological enhancements improving effectiveness, safety and convenience in treatment application.

In the short term, general factors such as earlier diagnosis and more effective treatment of PD and associated comorbid illnesses is likely to favorably impact the mortality of PD. With careful titration of Levodopa dosing and other adjunctive medications, the longevity of PD patients without dementia is likely to approach standard mortality, albeit in the elderly population. In the longer term, early efforts are underway to identify biological markers reflecting both the presence of disease (trait marker) and disease activity (state marker).

Richard Rougeau, M.D.

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MULTIPLE SCLEROSIS

Multiple Sclerosis (MS) is a progressive neurological disease of unknown cause, distinguishable by typical signs, symptoms and progression. The annual incidence is 11/100,000 persons, which has increased from 6.2/100,000 in 1984 and 1.2/100,000 in 1914 for reasons unknown. MS most commonly affects females (3:2), 20 to 40 years of age. I will briefly discuss the pathophysiology, etiology, symptoms, and diagnosis of MS. I will also discuss mortality and the underwriting methods one may use to properly evaluate individuals with MS for life insurance.

Pathophysiology and etiology

MS is caused by a loss of myelin, a process known as “demyelination.” Myelin, made of lipid and protein, is wrapped around the axons of nerve cells and allows rapid propagation of action potentials (the signals by which nerve cells communicate). Myelin synthesis starts in utero and essentially ends by the third year of life. Demyelination can occur from a variety of insults: viral infections, anoxic/ischemic injury, infection, nutritional disorders and leukodystrophies. The loss of myelin can also be idiopathic. When this happens once, it can lead to optic neuritis (see below). Recurrent idiopathic demyelination describes MS. The brain, optic nerves and spinal cord can all be affected, suffering scattered areas of demyelination and inflammation one millimeter to several centimeters in size. The periventricular white matter is the most likely area of brain involvement; in the spine the cervical region is most typical. Demyelination results in “white spots” on CT or MRI of affected regions.

The initiating cause of the demyelination that leads to MS is unknown. Most authorities feel there are environmental and genetic factors behind this idiopathic loss of myelin. Outbreaks of MS and uneven geographic distribution (more in the temperate zones) support the former; family clustering and association with certain class II MHC allotypes support the later.

It is clear that the pathogenesis involves immune-mediated inflammatory demyelination. Supportive evidence of this include the immunologic abnormalities found in the blood and CSF of MS patients, the association between MS and certain MHC class II antigens, and the clinical response of MS to immunomodulation. Symptoms of the disease improve with immunosuppression (prednisone, interferon-beta) and exacerbate with immune stimulation (interferon-gamma). Typical of other immune-mediated disease, intercurrent infections increase signs and symptoms; and while pregnancy improves the clinical course, MS often worsens after delivery.

Diagnosis

MS is a clinical diagnosis: progressive neurological symptoms in an appropriately aged patient, two or more CNS white-matter lesions on CT or MRI, and no alternative explanation for these findings. Younger patients often present with subacute or acute focal neurological signs, which vary depending on the region of the CNS involved. Optic nerves, pyramidal tracts and posterior columns of the spinal cord, the cerebellum and vestibular system can all be involved to various degrees. Older MS patients will present with a progressive myopathy. Leg weakness, axial instability and bladder impairments are typical findings in this group. Seventy percent of MS patients will improve after the initial bout, but with time, recovery from each attack decreases and fixed impairment results. After 10 years, half of MS patients are unable to carry out household and employment tasks; after 25 years, half are unable to walk. Thirty percent of all MS cases follow a chronically progressive course, especially in those persons over 45 years of age.

As MS is a clinical syndrome, laboratory and imaging studies only support, not make or confirm, the diagnosis. In addition to neuroimaging via CT and MRI, cerebral spinal fluid analysis can support the diagnosis (in MS the CSF has increased immunoglobulin levels.) Oligoclonal bands are found in up to 80% of MS patients. This is sensitive, but not very specific, for MS. Finding free kappa light chains in the CSF is more specific to the diagnosis of MS, but not as sensitive a test. CSF protein levels are overall, normal (elevated values imply a disease other than MS.)

Optic neuritis is an acute or subacute partial or complete loss of vision in one or both eyes due to inflammation of the optic nerve(s). Many people diagnosed with optic neuritis will eventually develop MS, and neuroimaging is very useful in this situation. If the brain MRI in patients with optic neuritis is consistent with MS, 35% of these people will develop MS within two years, and 85% within five years. On the other hand, if the MRI is normal, there is less than a five-percent chance of developing MS within five years.

Underwriting MS

The overall mortality of MS has been evaluated. In Los Angeles, 1,488 MS patients were followed and 10-year mortality rates were found to be 240% in males and 425% in females. In Washington state, 815 patients had 10-year mortality rates of 170% in males and 275% in females. Both regions had higher excess mortality in persons less than 40 years of age. The Canadian Institute of Actuaries stratified patients with MS by age, and compared mortality to other insured lives. These results are summarized in Table 1.

Table 1. Life expectancy, expressed as years remaining, in insured individuals with and without MS in males and females.

Age (y)	Female		Males	
	Insured	MS	Insured	MS
30	50	43	45	38
40	40	34	36	29
50	31	25	27	20
60	22	17	18	13

MS is unpredictable at best. There are, however, features that can help stratify cases. Favorable factors include a high degree of recovery after the first attack, a preponderance of sensory symptoms and a benign condition after the first five years of MS. Unfavorable findings include progressive disease from the outset, a preponderance of motor and cerebellar symptoms, and an MRI clearly consistent with MS at the time of initial symptoms. Use extreme caution in MS patients with significant depression.

Like most impairments, mortality of MS is affected by the severity of the disease. Thus it is very important to gauge the degree of impairment. The Kurtzke Expanded Disability Score is a detailed neurological physical evaluation, which can be used to stratify MS patients by severity of disease. Mild MS has a Kurtzke Score of 0 to 2.5, moderate MS a score of 3.0 to 4.5, severe MS 5.0 to 6, while a Kurtzke Score of over 6.5 relates to very severe MS. More importantly, the Kurtzke Score has been shown to correlate with mortality (Table 2). The Kurtzke Score, if available in the APS, should be utilized in underwriting of MS.

Table 2. Mortality Ratio correlates to the Kurtzke Expanded Disability Score in 2,348 patients over a 10-year period.

Kurtzke Score	Mortality Ratio
0 - 3.5	1.60
4.0 - 7.0	1.84
>7.5	4.44

If no recent Kurtzke score is available, one must analyze the APS and application to assess the severity of MS to determine if excess mortality exists. One method is to divide symptoms into broad organ systems: motor and coordination, sensory, mental, visual and brainstem, and bowel and bladder. Most, if not all deficits in these systems, may be assessed as mild, moderate, severe or very severe. By looking at multiple types of symptoms, rather than just focusing on, for example, ambulation, one can better gauge the overall severity of MS. The global risk can then be thoroughly, fairly and consistently determined. Table 3 is a representative scheme one may use to determine the severity of MS in an individual.

Table 3. Stratification of MS severity by organ systems.

Organ System	Mild	Moderate	Severe	Very Severe
Motor and Coordination	No disability Mild Ataxia	Unilateral assistance Truncal/Limb Ataxia	Bilateral assistance, Use of wheelchair Severe ataxia	Restricted to bed or wheelchair
Sensory	Normal Decrease in vibration sensation	Some loss of pain/position sensation	Significant loss of pain/position sensation in 2 or more limbs	Marked loss of pain/posi tion sensation
Bowel and Bladder	Normal Mild Urgency/Retention	Moderate urgency Frequent incontinence	Catheterization	Loss of bowel/bladder control
Visual and Speech	Normal to 20/60 Corrected Vision	Nystagmus, or <20/60 corrected vision	Marked nystagmus <20/200 corrected vision	Marked dysarthria, or Inability to swallow “Chronic brain syndrome”
Mental	Normal Mild Mood Alteration	Some decrease in menta- tion	Significant decrease in mentation	Significant Depression

The other factor in underwriting is the duration of disease. The initial symptoms may precede the diagnosis of MS by months to years. The longer one has had symptoms, the more comfortable the underwriter can be about the progression and overall prognosis. Use caution in the younger patients, as typically the duration of disease usually correlates with the clinical pattern of progression, i.e., the longer one has MS, the more likely one is to eventually develop a progressive pattern of disease.

Robert Profumo, M.D.

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SEIZURE DISORDERS TYPES AND TREATMENTS

There are more than two million people in the U.S. diagnosed with seizure disorders. Seizure disorders can begin at any age, although they are more prevalent in children and young adults. These disorders generally do not get worse with age. There are many causes of seizures, including brain injuries, toxins, structural abnormalities in the brain including tumors, high fever in children, and illnesses. However, in most people diagnosed with seizure disorder (defined as having more than one seizure), a cause is not found.

Seizures result from inappropriately signaling nerve cells, called neurons, in the brain. Normally, signals are sent from neuron to neuron using electricity. When a neuron is stimulated, it releases a substance called a neurotransmitter, which in turn causes adjacent cells to be stimulated, resulting in an orderly flow of information. When something goes wrong in this process, electrical signals can be disordered and magnified, resulting in a seizure. A person with a seizure disorder is susceptible to these disturbances. It appears that this susceptibility can be inherited, and several genes have been identified as associated with certain seizure types. What follows is a summary of the different types of seizures, and how they are managed.

Partial vs. Generalized Seizures

In a partial seizure, the electrical disturbance is confined to a specific part of the brain, whereas in a generalized seizure the disturbance affects the entire brain. Sometimes, what begins as a partial seizure goes on to spread to the entire brain. These are called partial seizures, secondarily generalized. Partial seizures are more common in adults, whereas generalized seizures are more common in children.

Types of Partial Seizures

Simple Partial Seizures In simple partial seizures, patients do not lose consciousness. They are aware that they are having a seizure and remember what happened. Simple partial seizures can affect parts of the brain involving movement, emotion or sensation. For example, a seizure may result in uncontrolled twitches of a body part, a sudden feeling such as fear or joy, or a strange taste or alteration in perception.

Complex Partial Seizures In complex partial seizures, there is an alteration of consciousness; the person cannot remember what happened during the seizure. These seizures are also called psychomotor epilepsy or temporal lobe epilepsy, as they often originate in the temporal lobes of the brain. During this type of seizure, the person stares and repeats an action over and over, such as buttoning and unbuttoning a shirt.

Types of Generalized Seizures

Tonic Clonic Seizures These seizures are also called Grand Mal. They often begin with an aura, so persons are aware that they are about to have a seizure. This is followed by the tonic phase, where the person loses consciousness completely, the body stiffens up, and they fall to the ground. Shortly thereafter, the limbs begin to jerk (the clonic phase). Generally this lasts a few minutes, after which the person regains consciousness, but may be confused.

Absence Seizures Absence seizures are also referred to as Petit Mal seizures, and as the name suggests, are much less dramatic than tonic clonic seizures. These consist of a brief loss of consciousness, during which the person stares blankly, then quickly regains awareness.

Myoclonic Seizures These seizures come on suddenly, and consist of giant muscle spasms, either of the whole or parts of the body. The person may or may not lose consciousness. This type of seizure is much less common than those previously described.

Atonic Seizures Also called drop attacks, in this type of seizure the person loses consciousness and drops suddenly to the ground. Usually, consciousness is quickly regained.

Treatment of Seizure Disorders

When other, treatable underlying causes for seizures have been ruled out (such as an operable tumor), the first line of defense against seizures is oral medications, such as the commonly used drugs Dilantin, Tegretol, and Depakote. Sometimes more than one drug is necessary to eliminate seizure activity, although it is preferable to take only one anti-seizure drug. Blood levels of these drugs need frequent monitoring, as high levels can be toxic.

If drug treatment fails, surgery may be a successful way of eliminating seizures. Surgery is only performed when a person has partial seizures, originating in a part of the brain that is not crucial to the individual's functioning.

An alternative treatment used in children who have intolerable side effects from medications is the ketogenic diet. This is a carefully proportioned diet that is high in fat. This causes the body to use fats instead of glucose for energy, a state called ketosis. In many children, the diet can reduce or eliminate seizures, with fewer side effects than medication.

Vagus nerve stimulation (VNS) is accomplished by surgically implanting a battery connected to the vagus nerve in the chest wall. The battery sends regular pulses of electricity into the brain via this nerve. When a seizure is coming on, the battery may be turned on and off by a magnet. Although VNS often doesn't eliminate all seizures, it can improve control in individuals resistant to drug treatment.

TUMORS OF THE CNS AN OVERVIEW

The human central nervous system (CNS), like all tissue, is susceptible to neoplastic growths, both benign and malignant. While other organ systems offer their own diagnostic and therapeutic challenges, the CNS has two additional impediments to early diagnosis and treatment—the cranium and the blood-brain barrier. The cranium, while vital for the protection of the vulnerable brain, interferes with both early diagnosis and therapy, and the blood-brain barrier hampers effective treatment. Fortunately, once the index of suspicion for a CNS tumor has been raised, newer investigative modalities can lead to a speedier uncovering of the tumor. Likewise, inroads have been made in overcoming the defenses of the blood-brain barrier.

CNS tumors are relatively rare. Malignant tumors account for 6.5/100,000 persons per year and benign tumors account for 5.3/100,000 persons per year. It has been estimated by the Surveillance, Epidemiology, and End Results (SEER) program that there are about 17,000 new cases of CNS cancers annually in the U.S. There are also about 13,000 CNS cancer deaths per year. Clearly, CNS cancer is a disease with a dismal prognosis. Cancer of the CNS remains the second leading cause of cancer death in those under 15 (leukemia is first). The incidence of CNS malignancies also appears to increase with increasing age. Although many people succumb to cancer of the CNS, there are survivors, and life insurers must be familiar with this dangerous disease in order to appropriately select insurable risks. 'Benign' tumors of the CNS possess their own unique hazards, since some have a tendency to recur, and many are difficult to totally excise.

The World Health Organization (WHO) classifies CNS tumors into nine categories:

Tumors of neuro-epithelial tissue, Tumors of the cranial and spinal nerves, Tumors of the meninges, Hematopoietic neoplasms, Germ cell tumors, Cysts and tumor-like lesions, Tumors of the anterior pituitary, Local extensions from regional tumors, Metastatic tumors

There are 22 separate cancers arising from neuro-epithelial tissue, with additional sub-categories. It is beyond the scope of this article to discuss all the benign and malignant variants of CNS tumors. Instead, I will focus on two entities: astrocytomas and meningiomas. These lesions are relatively common examples of both malignant and benign lesions that are encountered in medical underwriting. Some of the specifics pertinent to these lesions can be applied to other types of CNS tumors.

Evidence of CNS tumors may include general signs and symptoms such as headache, nausea and vomiting, and changes in consciousness. Fortunately, these signs and symptoms are rarely due to tumors, but usually to more common conditions with little extra mortality. Other signs and symptoms of space-occupying lesions in the CNS may help localize a lesion to a particular area of the brain. Magnetic resonance (MRI) imaging of the brain is the current gold standard for investigating the presence of brain tumors and measuring response to treatment. It is largely replacing the CT scan due to its superior imaging qualities. Positron emission tomography (PET) is a useful tool used to evaluate the metabolic function of the brain. Malignant tumors are generally hypermetabolic compared to normal brain tissue, whereas radiation-damaged or necrotic brain reveals reduced metabolic activity. The PET scanner utilizes this fact to help physicians diagnose brain tumors and evaluate the post-treatment state. Magnetic Resonance Spectroscopy (MRS) also measures intracellular metabolites in order to correlate abnormal metabolic activity with the presence of tumors.

The accurate diagnosis of CNS tumors requires surgical biopsy. Typically the only exception to this rule is in the case of tumors of the pons and medulla where tumors are predominantly higher grade astrocytomas and the outcome is not improved by biopsy. In most cases, an attempt at complete resection of the tumor is recommended, assuming it is surgically feasible. In some cases this may allow cure, but at the very least, surgical debulking aids in the resolution of symptoms. Depending on the nature of the tumor, adjuvant radiotherapy or chemotherapy may extend survival. Stereotactic radiosurgical techniques, such as the Gamma knife, may be used for small-localized lesions.

Astrocytomas

The term 'glioma' is used to describe a neoplasm that is derived from any of the cells that form the interstitium of the CNS. These cells provide the glue that binds the basic physical structure of the CNS. The most common glioma is known as the astrocytoma. Astrocytomas comprise about 75% of adult gliomas and are composed of cells called astrocytes. The pathological grading of these tumors is usually based on either the three-tier WHO system or the four-tier Daumas-Dupont system. Each system rates the tumors histologically, based on variables such as degree of cellularity, nuclear and cellular pleomorphism, mitotic figures, endothelial proliferation and necrosis.

Grade I tumors are the least abnormal histologically and are called astrocytomas. Grade II are more bizarre and are termed anaplastic astrocytomas. The most bizarre lesions are known as glioblastoma multiforme and are either Grade III or IV. In general, it is usually only the survivors of low-grade or very well differentiated astrocytomas (Grade I) who present for insurance purposes. Long-term survival from higher grade astrocytomas is relatively uncommon.

Mortality studies on low-grade astrocytomas reveal that complete surgical resection is necessary for cure. Post surgical radiation following complete resection increases the likelihood of long-term survival. Younger ages (<40) clearly do better than older patients. Location of the presenting tumor is also a factor, with those in the cerebellum doing the best, followed by supratentorial lesions and, at a distant third, those in the brain stem. Most late deaths are due to recurrence, and as is true of all grades of astrocytomas, a propensity to transform into higher grade tumors.

Meningiomas

In the case of tumors of the CNS, the word 'benign' does not have the same significance as in other areas of the body. So-called benign meningiomas, unlike most other benign tumors elsewhere, may invade other tissues. They also tend to recur even if excision appears complete, and can cause death by bleeding, or compressing other contents of the cranium. Meningiomas arise from arachnoidal cells in the meninges. They comprise almost 40% of CNS tumors and occur both in the brain and spinal cord. Most meningiomas are well differentiated, with limited potential to invade surrounding neural tissue. Symptoms of a meningioma are usually secondary to compression of surrounding structures. Although meningiomas represent 'benign' variants of CNS tumors, they do pose extra mortality risk since they tend to compress vital areas, are very vascular and may present serious obstacles to total excision. Recurrence rates have been estimated to be anywhere from 9% to as high as 32% over a 15-year period. Extra mortality from meningiomas is lowest in the elderly, possibly because most of the benign forms are very slow growing.

While most meningiomas seen for underwriting purposes are relatively benign in histological appearance, there are two other categories of meningiomas. 'Atypical' meningiomas show clear evidence of brain invasion and have a much worse prognosis than most benign meningiomas. Malignant meningiomas (sometimes known as anaplastic meningiomas) show invasion into brain tissue and also demonstrate high levels of mitotic activity. These tumors are quite aggressive, with a poor outcome if left untreated. Treatment ideally consists of complete surgical resection with additional radiotherapy. Subtotal resection of atypical anaplastic meningiomas is associated with mortality rates generally unsuitable for insurance coverage. Chemotherapy is usually reserved for intransigent recurrences.

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