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REVIEW ARTICLE

Multiple sclerosis: basic knowledge and new insights in perioperative management

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Abstract Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system affecting young adults that may lead to significant disability. The clinical course varies among the types of the disease as well as among individuals. Herein we provide a brief review of the recent data concerning the clinical presentation, diagnosis, causes, and pathogenesis of MS as well as medication used, followed by the anesthetic considerations of patients diagnosed with the disease. To accomplish this, we conducted a systematic PubMed literature search for articles, using the terms multiple sclerosis, anesthesia, general, regional, perioperative, and preoperative, and we then manually reviewed the references from each pertinent article. Because randomized controlled trials on the field are rare, most information is derived by case reports and case series. We concluded that the disease itself as well as the treatment modalities may have several implications in the conduct of anesthesia and perioperative management of MS patients. General and regional anesthetic techniques have been successfully used. With thorough preoperative evaluation and in depth knowledge of the disease and its complications, the MS patients can be managed safely.

Keywords Multiple sclerosis · General anesthesia · Regional anesthesia

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Introduction

Multiple sclerosis (MS) is a chronic disabling demyelinating inflammatory disease of the central nervous system (CNS), characterized by variable course and severity. It was first described in 1868 under the name "sclerose en plaques" by Jean Martin Charcot, who attributed to the disease the currently known as Charcot's neurological triad (nystagmus, intention tremor, and staccato speech) [1]. Throughout the 20th century several investigators performed studies in an effort to explain the cause and pathogenesis of MS, but effective treatments only began to appear in 1990 [2].

The prevalence of MS ranges between 2 and 150 per 100,000, depending on the country or specific population, and is highest in Europe, southern Canada, northern United States, regions of Australia, and New Zealand [3]. Women are predominantly affected, with a female-to-male ratio of 1.4–2.3, with evidence suggesting an increasing trend over time in women even though a controversy exists as to whether it is a true increase or the result of better detection methods [4]. The mean age of onset is 30 years, but rarely onset can occur as late as the seventh decade [5].

Methods

Two investigators conducted a systematic PubMed literature search (1980–March 2013) for articles using the terms multiple sclerosis, anesthesia, general, regional, perioperative, and preoperative. This initial search revealed 495 articles that were examined for relevance. A manual review of references from each pertinent article was also carried out to identify additional related articles. Much of the

literature is in the form of case reports and case series as randomized controlled trials on the field are rare.

Background

Clinical presentation, causes, and pathogenesis of MS

The main feature of MS is a variable neurological dysfunction showing characteristic relapses and remissions. Three main types are defined according to the natural history of the disease: relapsing remitting MS (RRMS), which is the most common, including almost 90 % of the patients affected, primary progressive MS (PPMS), and secondary progressive MS (SPMS) [6]. RRMS is characterized by relapses separated by defined intervals during which there may be full recovery, or some residual deficits, but no disease progression. The PPMS form has a progressive course starting from the onset of the disease, whereas the SPMS starts as an RRMS disease and then shows a progressive pattern that may include relapses and remissions [7].

Symptoms vary depending on the nerve fibers affected. As known, among the commonest initial clinical manifestations are visual disturbances, almost always unilateral, including partial or complete vision loss (scotoma), painful eye movements, and double or blurred vision: these are manifestations of optic neuritis. Sensory deficits involve numbness, tingling, or itching of the extremities or the trunk. Impairment of facial sensation, trigeminal neuralgia, hemifacial spasms, and facial myokymia (fine unilateral involuntary rippling of facial muscles) may also occur. Tremor, scanning speech, coordination defects, nystagmus, and unsteady gait may appear mainly because of cerebellar involvement [8]. Motor deficits, the result of descending motor pathway involvement, include paraparesis or paraplegia and less often upper extremity weakness. Spasticity of the extremities, increased deep tendon reflexes, and disuse amyotrophy may also be present [8, 9]. Other less characteristic symptoms include intestinal or bladder dysfunction, cognitive impairment, increased incidence of epilepsy (occurring in 2–3 % of patients, the result of abnormal electrical activity of demyelinated neurons) and fatigue. The latter is often seen during an acute attack and characteristically may precede and last beyond the attack [9, 10]. MS is characterized by an increased incidence of depression, bipolar disease, or other psychiatric manifestations. Prevalence of major depression ranges from 19 to 54 % [11].

Pain is a common feature. MS predisposes to nociceptive, neuropathic, psychogenic, idiopathic, and mixed types of pain as a result of lesions in spinothalamo-cortical pathways, ectopic discharges by demyelinated neurons, activation of intraneural nociceptors, postural anomalies secondary to motor disturbances, and spasticity. Continuous burning extremity pain, migraine, back pain, and painful tonic spasms are common [12]. Lhermitte's sign, which consists of a painful transient electric-like shock sensation extending down the spine and the extremities triggered by neck flexion, may appear in as many as 40 % of patients [13].

Both environmental risk factors and genetic susceptibility have been implicated as the cause of the disease. As to environmental factors, an association between MS and latitude has been suggested, with disease prevalence increasing with geographic latitude, although this difference is being attenuated over time [4]. White populations and developed countries are associated with greater incidence [14]. Other possible environmental factors include viral infections (particularly Epstein–Barr), smoking, decreased sun exposure, and vitamin D deficiency [15–18]. Genetic studies have implicated a number of immunologically relevant genes. A variation within the major histocompatibility complex plays a major role, and more than 20 risk loci have already been identified [19]. In fact, Goodin, using a mathematical model to describe the causal pathway leading to adult MS, concludes that genetic susceptibility is actually the most important factor in the pathogenesis [20]. Interestingly, occupational exposure to anesthetic agents does not seem to increase the risk of developing multiple sclerosis [21].

Recent data suggest that the innate immune system plays a major role in the initiation and progression of the disease through the modification of T- and B-lymphocyte function. An adaptive immune response is also involved, through activation of CD4 and CD8 cells and their polarization to Th1 and Th17 effector cells, as well as cytokine formation (interleukins 17 and 22) that may damage the blood–brain barrier, allowing the autoreactive lymphocytes to gain access to the central nervous system (CNS). These complex pathways subsequently lead to demyelination and axonal loss, causing exacerbations of the disease [22, 23]. During remissions, waning of the inflammation and remyelination take place. Disease progression is caused by incomplete or no remyelination and axonal degeneration, which cannot be reversed, leading to permanent neurological deficits [2].

Diagnosis and treatment of MS

Because disease-specific clinical features are absent, except the aforementioned disease-characteristic Lhermitte's sign and the Uhthoff phenomenon (worsening of neurological symptoms and signs with increasing body temperature as after exercise or fever), diagnosis is almost always supported by imaging and laboratory studies [2, 24]. The McDonald criteria, revised in 2010, are often used for diagnosis (Table 1) [25].

Table 1 The 2010 revised McDonald criteria for multiple sclerosis (MS) diagnosis [25]

Clinical presentation	Additional data needed for diagnosis
Two or more attacks; objective clinical evidence of two or more lesions or objective clinical evidence of one lesion with reasonable historical evidence of a prior attack	None
Two or more attacks; objective clinical evidence of one lesion	Dissemination in space, demonstrated by one or more T2 lesion(s) in at least two of four MS-typical regions of the CNS; or await a further clinical attack in a different CNS site
One attack; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack
One attack; objective clinical evidence of one lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: one or more T2 lesion(s) in at least two MS-typical regions of the CNS; or await second clinical attack in a different CNS site; and For DIT: simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression plus two of the following criteria: 1. Evidence for DIS in the brain based on one or more T2 lesion(s) in the MS-characteristic regions 2. Evidence for DIS in the spinal cord based on two or more T2 lesions in the cord 3. Positive CSF

MS multiple sclerosis, *CNS* central nervous system, *MRI* magnetic resonance imaging, *DIS* dissemination in space, *DIT* dissemination in time, *PPMS* primary progressive multiple sclerosis, *CSF* cerebrospinal fluid, *T2 lesions* hyperintense lesions appearing as bright spots on the MRI image

Management of MS is multidirectional, aiming at alleviating symptoms, reducing attack frequency and shortening the duration of the attacks, minimizing neurological deficits, and finally preventing the progression of the disease. As endpoints to evaluate drug efficacy, the suppression of relapses and their surrogates (new lesions on MRI) are used. The pivotal studies for licensed therapies of MS are usually small and do not provide data on long-term efficacy and side effects [2]. First-line treatment agents are used after diagnosis and basically for the RRMS form, whereas a second-line drug is used when failure or intolerance of prior first-line treatment is observed or for highly progressive disease.

Immunomodulatory therapy consists of interferons (mainly interferon β-1b and interferon β-1a) and glatiramer acetate as first-line medications, mainly for the RRMS form, and natalizumab and fingolimod are used as second-line treatments [26, 27]. Interferon therapies were started on the basis that their antiviral properties might reduce the environmental triggers of MS [2]. A great aspect is their relatively innocuous profile. However, up to one-third of patients develop antibodies during the first year of therapy with a subsequent reduction in effect [28]. Glatiramer is believed to act through tolerance induction of myelin-reactive lymphocytes [29].

Immunosuppressive treatment demonstrates limited efficacy and considerable toxicity. Consequently, it may be reserved for aggressive MS as described by a retrospective study in which the use of cyclophosphamide followed by maintenance therapy using glatiramer had some positive effects [30]. Management of acute attacks depends on severity, but in general high-dose steroids, IV immunoglobulins (IVIG), and plasmapheresis are considered [6, 23]. IVIG has been recently questioned [31]. Recent guidelines published in 2011 by the American Academy of Neurology suggest that plasmapheresis is possibly effective and should be considered as second-line therapy in steroid-resistant relapsing forms of MS [32]. In 2010, 4-aminopyridine (4-AP) received approval for ambulatory patients. 4-AP acts by selectively blocking voltage-gated potassium channels, prolonging the action potential and increasing calcium influx [33]. Through these properties it has the ability to improve conduction and synaptic transmission in demyelinated neurons. Mitoxantrone, which acts by inhibition of DNA and RNA synthesis, is reserved for rare difficult cases because it can cause cumulative cardiotoxicity and acute leukemia [34].

Apart from medication used for the treatment of the disease itself, MS patients are given several other therapeutic agents aiming at alleviating specific symptoms.

Baclofen is usually administered to regulate spasticity. To this end, dantrolene can also be prescribed [35]. Urinary incontinence is managed with tolderodine or oxybutynin. Common pain relief is offered, together with medication for neuropathic pain including pregabalin, gabapentin, carbamazepine, and amitriptyline [26]. Recently, the endocannabinoid system modulator delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) in the form of a mucosal spray has been tested for refractory neuropathic pain relief, with conflicting results: some benefit was shown but with a large number of placebo responders [36]. Tremor is treated with carbamazepine and propranolol.

Anesthesia and MS

Drugs used in MS and anesthesia

Medications used in MS may complicate anesthesia. In Table 2, adverse effects of the aforementioned agents that may affect anesthetic practice are described.

Baclofen may cause muscle weakness, rendering the patient extremely sensitive to the action of nondepolarizing muscle relaxants. When stopped abruptly it may lead to agitation, delirium, and convulsions; therefore, a 2-week gradual withdrawal is advised [37, 43].

Regarding emergency surgery during disease exacerbation, replacement therapy should be considered if patients are on high-dose corticosteroids, ensuring they receive their current dose perioperatively [44]. IVIG can cause some transient adverse reactions soon after infusion, such as headaches, tachycardia, hypotension, and wheezing, but some rare side effects may considerably complicate anesthesia: thromboembolic events, acute renal dysfunction, and acute myocardial infarction. Additionally, patients may be infected by viruses such as hepatitis and human immunodeficiency virus (HIV) after exposure to virally contaminated IVIGs [45]. Following plasmapheresis, fever, urticaria, hypotension, and hypocalcemia (citrate anticoagulant induced) may occur [46].

There are no data as to whether it is prudent to discontinue treatment of MS for surgery. It is important to mention, however, that several studies and case reports describe disease recurrence days or months after discontinuing MS treatment [47, 48]. In a study of 43 patients who discontinued their interferon-β treatment, 20 % of them showed a resurgence of disease activity, defined by the appearance of new, or worsening of existing, neurological symptoms lasting at least 48 h within 30 days [49]. A common feature of all studies is that relapses are particularly evident in patients with a highly active disease. Decision on discontinuation before surgery should be based on the presence of side effects and how these could complicate anesthesia. Consultation with a neurologist should be sought in difficult cases. If medication is discontinued, it should definitely be restarted as soon as possible.

Preoperative evaluation

Making a decision on the type of anesthesia necessitates a detailed history and clinical examination, which should identify the type of MS from which the patient suffers, the presence of acute exacerbation, current medications, and the degree of neurological impairment, especially when regional techniques are being considered.

A crucial aspect of anesthetic practice is the existence of respiratory dysfunction, which is often a characteristic of the end stages of the disease, but may as well appear in earlier stages [50, 51]. In one study, respiratory dysfunction of variable degrees was documented in more than 80 % of nonambulatory and nearly one third of ambulatory MS patients, attributed mainly to lack of respiratory muscle coordination caused by cerebellar impairment [52]. Regarding pulmonary function tests, lower, but within normal limits, FEV1/FVC ratios have been found in MS patients without any disability compared to healthy controls, a difference that approached significance ($p = 0.06$), whereas 50 % of them had also lower, yet normal, maximal expiratory pressure (MEP). A significant lower diffusion capacity of the lungs for carbon monoxide (DLCO) was also documented [53]. In any case, clinical assessment is the most important initial tool as a predictor of respiratory muscle weakness and may be even superior to spirometry [54]. Clinical assessment should include ability to cough and clear respiratory secretions effectively and ability to exhale deeply [55]. Overall, preoperative respiratory assessment should be driven by the severity of the disease and the initial clinical assessment, together with the type of surgical procedure scheduled.

An increased incidence of obstructive sleep apnea (OSA) in MS patients has been suggested along with other less common sleep disorders such as central sleep apnea, death during sleep (Ondine's curse), insomnia, nocturnal movement disorders, and narcolepsy [56]. OSA may be associated with lesions in the higher centers regulating motor control of respiratory and airway muscles and obesity that may follow prolonged inactivity [57]. It may also be a side effect of drugs used for disease management, such as the GABA-B receptor agonist baclofen and the GABA-A receptor agonist clonazepam, which predispose to OSA by causing relaxation of the pharyngeal muscles [58]. Patients should be carefully evaluated for potential difficult airway, and use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure perioperatively to reduce hypoxic events should be considered [59].

Table 2 Implications of anesthetic relevance of drugs used in MS

Drug	Side effects with anesthetic relevance	Perioperative considerations
Interferon-β [37, 38]	Flu-like symptoms (fever, rigor, myalgias, fatigue) 24–48 h after injection	Careful evaluation to exclude respiratory infection or imminent disease exacerbation
	Abnormal blood count tests, including thrombocytopenia	Consider risks with neuraxial anesthetic techniques
	Elevated liver enzymes or even hepatitis	Consider anesthetic drug metabolism and clearance
Glatiramer acetate [37, 39]	Systemic reaction (chest discomfort, palpitations, dyspnea, tachycardia, flushing) appearing immediately after SC injection, lasting 10–20 min	N/A
	Hepatotoxicity	Consider anesthetic drug metabolism and clearance
	Progressive multifocal leukoencephalopathy	Associated with decreased immunity, vigilance for opportunistic infections
Natalizumab [40]	Bronchitis, bronchospasm	Careful preoperative clinical examination/lung auscultation
	Bradycardia	Careful ECG evaluation
	Deterioration of LVTs	Consider anesthetic drug metabolism and clearance
	Progressive, even lethal, multifocal leukoencephalopathy	Associated with decreased immunity, vigilance for opportunistic infections
Fingolimod [37, 41]	Chronic fatigue state	N/A
	Cardiac conduction changes, cardiomyopathy, bradycardia, AV block	Careful ECG evaluation/clinical examination/ exercise tolerance
	Elevated liver enzymes	Consider anesthetic drug metabolism and clearance
	Dyspnea including decreases in FEF	Careful preoperative clinical examination/lung auscultation
4-AP [33]	Dry mouth, diaphoresis, seizure activity, agitation, delirium	Clinical evaluation
	Cardiac involvement (hypertension, SVT, AF), theoretical risk of QT prolongation	ECG
		Avoid drugs that prolong QT
	Toxicity	Managed with benzodiazepines, anticonvulsants and supportive measures, including intubation
Cyclophosphamide [42]	Myelosuppression (leading to pancytopenia), pulmonary fibrosis, myocarditis	Check platelet count if considering neuraxial anesthesia
		Chest auscultation/X-ray
		Careful clinical cardiac evaluation
Mitoxantrone [34]	Cumulative cardiotoxicity	Careful clinical evaluation/consider echocardiography
	Acute leukemia	Evaluate full blood count

MS multiple sclerosis, *N/A* not available, *SC* subcutaneous, *LVTs* liver function tests, *AV* atrioventricular, *FEF* forced expiratory flow, *4-AP* 4-aminopyridine, *SVT* supraventricular tachycardia, *AF* atrial fibrillation, *NMBDs* neuromuscular blocking drugs

Autonomic nervous system involvement may implicate anesthetic management and should be identified in advance. The most important aspect to the anesthetist is the variable degree of hemodynamic instability, which could be superimposed on cardiovascular side effects of the medications already discussed [60]. Marked hypotension with reduced response to intravenous fluid or vasopressor therapy should be expected during induction. Patients may complain of orthostatic dysregulation that could be found in up to 25 % of cases, bladder or bowel dysfunction, neurocardiogenic syncopes, or cardiac dysrhythmias [61, 62]. Several tests have been advocated to assess the cardiovascular autonomic system, but their value in MS is questionable. Differences in Valsalva's maneuver, used as a parasympathetic test, between patients with active and inactive disease as well as abnormalities in heart rate variability during deep sleep, have been documented [62, 63].

Cardiac evaluation is of crucial importance as treatment may interfere with conduction or cause cardiovascular

instability, as mentioned. Clinical assessment should provide guidance for further testing. Liver function tests must also be carried out to identify any adverse effects of treatment.

Anesthesia and MS: general considerations

The main concern is disease exacerbation following anesthesia and surgery. There is no clear evidence that these two stressful procedures per se will cause an exacerbation, as any stressful situation may trigger one. As such, infection and inflammation, fever/hyperpyrexia, delivery, and emotional stress should also be encountered in the best possible manner.

Elevated body temperature is one of the most studied triggers. Uhthoff's study is still used as a hallmark reference describing the principle of conduction block in demyelinated axons after heat exposure [64]. A case of bilateral involvement of the hypothalamus in a patient with MS, related to the appearance of difficult-to-treat periodic hyperthermia up to 40 °C, has been described and could be one of the causes leading to death [65]. Continuous temperature monitoring and meticulous control in case of hyperthermia with antibiotics (if infective causes are suspected) or antipyretics, room temperature modification, cooling devices, and cool fluids administration should be used. Pseudorelapses (worsening of symptoms from sepsis/fever) in the perioperative period should be differentially diagnosed from real disease exacerbations. In these cases, treatment should aim at controlling infection.

There are multiple reports of successful use of both inhalational and intravenous anesthetic agents with no suggestion of preferable use of one over the other [66–73]. No complications have been reported with the use of either sevoflurane or desflurane or with nitrous oxide [67, 73, 74]. Midazolam can be used as a premedication, with special caution in patients with respiratory compromise [73]. Actually, premedication can be particularly advantageous in reducing stress before surgery, considering that stress is a triggering factor for disease exacerbation. Midazolam has also been administered for induction of general anesthesia at doses of 0.2–0.3 mg/kg, and its minimal effect on thermoregulatory control is a property very important in MS patients [74]. It is suggested that midazolam may actually even reduce core body temperature through inhibition of tonic thermoregulatory vasoconstriction [75]. Recently, dexmedetomidine for monitored anesthesia care at a bolus dose of 1 μg/kg followed by infusion at 0.5 μg/kg/h has been reported. Patient satisfaction was reported to be high, but hypotension and bradycardia were documented as expected [76]. Finally, almost all opiods have been administered intraoperatively in patients with MS [67, 73]. Nevertheless, they should be used judiciously, especially in patients with suspected respiratory compromise.

Special attention is needed with the use of neuromuscular blocking drugs (NMBDs). In patients with MS an upregulation of nicotinic acetylcholine receptors of skeletal muscles is noted. In addition, a constitutional change of the receptor subunits leading to prolonged duration of channel opening is seen [77]. Although succinylcholine has been given in patients with MS, the risk of producing hyperkalemia is evident and may be even more accentuated during exacerbations [78]. The succinylcholine risk of hyperkalemia has also been correlated to progressive disease [79]. A case of life-threatening hyperkalemia during an exacerbation of MS has been described recently [80]. The preoperative potassium level was 3.7 mEq/l, and the first potassium concentration measured after the event and after therapeutic measures were started was 6.7 mEq/l. Patients are at risk for hyperkalemia from the fourth day of the symptoms onset until months or even years later, even if no new symptoms appear; no safe time interval between relapses for the use of this agent has been described [81]. Therefore, succinylcholine should best be avoided. Even though resistance to nondepolarizing NMBD has been reported in the past, it does not seem to occur very often as normal response has been described in several cases [67, 73, 74, 82–84]. An increased number of postjunctional receptors explains the relative resistance to these agents; muscular weakness and decreased muscle mass may be responsible for the cases of increased sensitivity [72, 84]. Because of the unpredictable response to non-depolarizing NMBDs it is imperative to carefully titrate the dose administered. Neuromuscular monitoring preferentially in a nonaffected or the least affected limb is advised.

Deep brain stimulation is been used lately as a treatment modality for tremors and chronic pain and carries additional anesthetic considerations. Intraoperative electrophysiological guidance through microelectrode recording (MER) is used to locate the targeted nuclei. Propofol is the most common intravenous agent used, but there is limited information regarding the impact of anesthetic agents on MER [85]. Monitored anesthesia care is preferred as awake patients can facilitate target nuclei localization. Apart from propofol, dexmedetomidine could also be used with special attention for delayed awakening. Reducing stress is of great importance. To this end, benzodiazepines could be considered. Complications of the procedure include respiratory depression resulting from sedation or intravascular events, such as seizures and hemorrhage. Arterial blood pressure elevation should definitely be avoided to minimize the risk of bleeding. Perioperative seizures or extremity weakness should be differentially diagnosed. Most seizures do not seem to require treatment as they are transient, but if they do occur, midazolam and propofol can be used [86]. Last,

venous air embolism represents a rare complication of the procedure.

Electroconvulsive therapy (ECT), under general anesthesia, is increasingly used to treat severe or medication-resistant forms of depression [87]. Succinylcholine, often used as a short-acting agent, should best be avoided as described earlier, even in small doses. However, Fitzsimons and colleagues have presented a patient who received 25 ECTs using succinylcholine, in doses ranging between 50 and 70 mg, 4 years before being diagnosed with MS plus 27 more therapies after diagnosis, in doses ranging between 30 and 50 mg, before the appearance of serious neurological compromise, without any complication. After progression of the disease mivacurium was used for the subsequent ECTs, which represents a useful alternative because of its short duration [88]. Doses of 0.15 mg/kg are advised. Rocuronium and vecuronium, with the option of sugammadex reversal, are good alternatives [89]. Exacerbation of already established autonomic dysfunction is an additional concern. Adjuncts such as atropine or glycopyrrolate to control parasympathetic effects, β-blockers such as esmolol and labetalol, α2 agonists, Ca blockers, and nitrates (in patients at risk for myocardial ischemia) to control deleterious sympathetic effects must be readily available [89]. Temperature control does not seem to be a problem, as studies report even a decrease in temperature [90]. No documented exacerbation resulting from ECT was found in our research.

MS and neuraxial anesthesia

The theoretical concern about neuraxial techniques is partly supported by studies on the pathophysiological mechanisms within the CNS. These studies relate symptoms of MS to the binding of certain oligopeptides, which possess an inherent sodium channel-blocking activity, to nerves. Such oligopeptides are found in an abnormally high concentration in MS patient CSF [91, 92]. One of these, the QYNAD pentapeptide, was proved to have an anti-excitatory effect on intact myelinated axons of rat nerves [91]. This blockade may be responsible for the negative symptoms of the disease such as muscle weakness. Local anesthetics share common physiological properties with the aforementioned oligopeptides, so they could as well cause MS symptoms when used for central blocks and especially subarachnoid blocks [92].

Despite the aforementioned mechanisms, epidural anesthesia is generally considered a safe technique and there is no evidence that the clinical course of the disease is affected by it [2, 93, 94]. The fact that local anesthetics, finally approaching subarachnoid space following epidural injection, have a low concentration (approximately one fourth of the epidurally administered concentration) could be a positive characteristic of epidural anesthesia [95]. Epidural block has been studied more extensively in the obstetric population. Even though it is considered safe indeed, there have been reports of possible disease relapse in the past [95–99]. However, the postpartum period itself is also characterized by increased incidence of relapse [97]. In one such case, bupivacaine 562.5 mg was administered over 15 h in a parturient, and this high dose might have been responsible, although the implication of labor and cesarean delivery cannot be ruled out [95]. Fortunately, full recovery was achieved a few days later. In a study comparing the relapse rate within 3 months between three groups of obstetrics patients receiving epidural, general, or local anesthesia, no difference in relapse rates between groups was noted, with the results being comparable to rates of postpartum relapse in the literature [100]. Interestingly, of those patients in the epidural group who had a postpartum relapse, three of five had received more than 0.25 % bupivacaine and two had received 2 % lidocaine. There are recommendations toward the use of the lowest possible doses of local anesthetics for central nervous blockades, although this carries the risk of insufficient analgesia [99, 101]. Hypotension following neuraxial blockades can be resistant to vasopressor therapy [78].

For subarachnoid anesthesia, controversy still exists [99, 101–105]. Some early reports describe an unmasking of the disease [106–108]. The type of symptoms described, such as oculomotor paralysis, even if accepted that they are caused by local anesthetics, are usually transient and completely reversible. Moreover, they do not necessarily correlate to documented disease exacerbation [106, 109]. Despite the initial reports, spinal block is not necessarily associated with worsening of the disease nowadays [110]. In an older case series involving nine patients receiving 14 spinals for urological surgery, no complications were observed, except one case of an exacerbation that was transient [93]. The rate according to the authors is similar to that of patients receiving general anesthesia. Martucci and colleagues administered a successful spinal anesthetic for cesarean section in a patient with MS with normal results regarding the level of block and the intensity and duration of anesthesia, with no exacerbation in 12-month follow-up [111]. Of course, the blood–brain barrier disruption in MS patients resulting from an immunologically mediated vasculopathy should be kept in mind, but its clinical relevance is unclear [102, 112]. A survey has been performed in the UK on the anesthetic technique that obstetric consultants would use in women with MS [113]. The majority are willing to perform either spinal or epidural anesthesia and analgesia, provided that full consent by the mother is given. For labor analgesia 79 % would perform a regional technique. Epidural anesthesia over spinal was preferred by 4 %. Concluding, MS is not a

contraindication to spinal anesthesia and the relapse rate does not seem to be as high as was considered in the past [78, 106]. Actually, the initial fear for spinal anesthesia has not remained consistent over the years [101].

Intravenous lidocaine, however, can be associated with worsening of MS symptoms, mainly from the eyes [114]. On the other hand, intravenous lidocaine and oral mexiletine have the ability to reduce the positive symptoms of the disease, such as spasticity, by the same blocking conduction properties, as positive symptoms are attributed to ectopic impulses [109]. In any case, extreme caution should be given to avoid any accidental intravenous absorption that would interfere with neuronal impulses.

When epidural blood patch to treat postdural puncture headache is considered, the theoretical risk of augmenting epidural pressure, thus interfering with axonal conduction, should be taken into account. Epidural blood patch has been recently carried out without any reported complications [115]. It is suggested, however, that blood should be injected slowly so as to minimize elevations in epidural pressure. Additionally, monitoring somatosensory evoked potentials to detect any impulse conduction defect should be considered [115].

MS and peripheral nerve blocks

MS is mainly described as a disease of the CNS. Nevertheless, peripheral nervous system (PNS) involvement has been reported in postmortem studies [116]. Changes in axonal excitability of both sensory and motor nerves have been described [117, 118]. The PNS lesion is that of the typical postinfectious inflammatory polyneuropathy [119]. The abnormality in motor axons has been attributed to increased slow potassium current and that of sensory axons to changing of the gating of fast potassium channels [120, 121]. On the other hand, extensive nerve conduction studies in 60 MS patients have been described, and abnormalities suggestive of demyelination were found only in 5 % of them [122]. Moreover, the clinical significance of PNS involvement is not yet clarified [123, 124].

Koff and colleagues described a severe brachial plexopathy after total shoulder arthroplasty and ultrasound-guided interscalene nerve block [125]. The final diagnosis, inflammatory brachial neuritis, possibly was attributed to the nerve block, suggesting a possible subclinical peripheral nerve pathology that was a predisposing factor to the subsequent autoimmune nerve injury [125]. In such cases of damage, surgical factors should be also sought before establishing a diagnosis [126, 127]. A case of prolonged duration of anesthesia has been reported, characterized by motor block in both lower extremities following a two-level paravertebral block for an inguinal hernia repair [128]. However, this was probably the result of central neural blockade with the characteristics of dense spinal anesthesia from the increased sensitivity of the spinal cord because of demyelination [128]. Abnormal uptake of local anesthetic by the demyelinated nerves has also been postulated. In contrast, femoral and sciatic nerve blocks have been administered for orthopedic surgery, with no relapse in 30-day follow-up noted; overall, despite the theoretical fears, peripheral nerve blocks are indeed far from the central lesions in MS and are considered safe [101, 129]. Moreover, the prolonged and efficient analgesia of nerve blocks provides a pain- and stress-free postoperative period, decreasing the possibility of exacerbations.

Adjuvants, such as epinephrine, should better be avoided so as not to cause an additional strain on the nerves through vasoconstriction [101]. Ultrasound-guided blocks are suggested by many. Even though ultrasound cannot abolish patient- and surgery-related risk factors, it could minimize anesthetic-related risks such as mechanical trauma and local anesthetic toxicity. Moreover, ultrasound guidance allows the use of lower volumes of local anesthetic (potential of reducing neurotoxicity), thus avoiding additional inflicting factors [130].

Conclusions

MS is a chronic demyelinating disorder of the nervous system with variable course, mainly showing relapses and remissions. The disease itself, as well as the medication used, may have various implications in anesthetic practice. Despite the longstanding perception that anesthesia may trigger an exacerbation or worsen the clinical status of MS patients, a thorough study of the literature is mostly reassuring, including the use of regional techniques. What is most important is the meticulous preoperative assessment and better knowledge of the disease's pathophysiological mechanisms as well as the effects of medications used for the management of the disease that may complicate perioperative management.

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