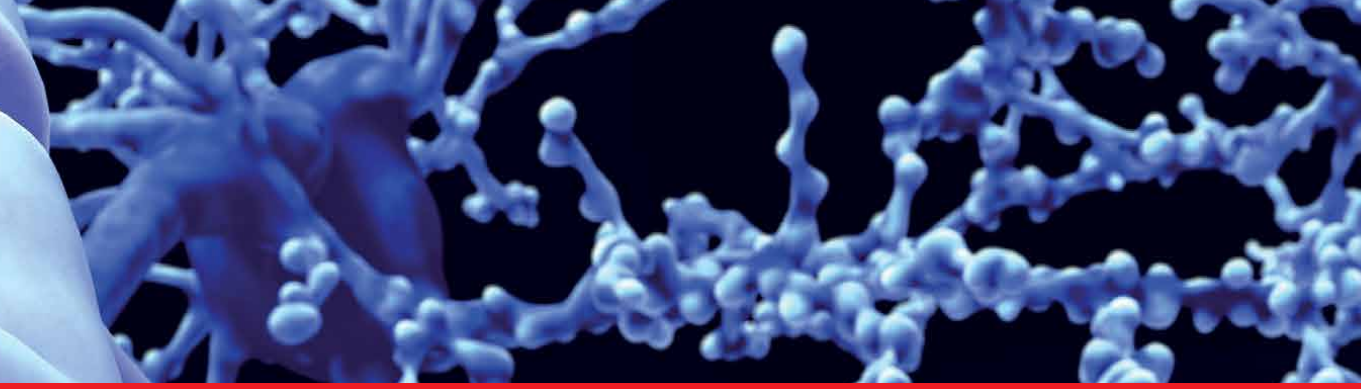

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Demyelination Disorders

Edited by Stavros J. Baloyannis, Fabian H. Rossi and Welwin Liu

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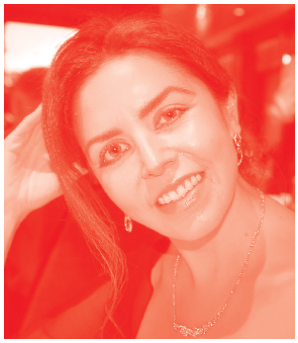

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Dr. Welwin Liu obtained her medical degree from the University of Maryland School of Medicine. She completed her neurology residency at Emory University, Georgia, and her fellowship in Clinical Neurophysiology at Temple University, Pennsylvania. She is board certified in neurology and has been a VA staff neurologist for more than 21 years. She is currently working at the Spark M. Matsunaga VAMC in Honolulu, HI where she has also performed duties as acting chief of neurology. She has co-authored multiple articles and received numerous awards.

Contents

Preface

Demyelination disorders are among the most frequent neurological conditions that affect either the central or the peripheral structures of the nervous system or non-rarely both of them. These disorders have a multifactorial causative background and result in serious physical incapacity. They induce suffering, physical inability, and psychological and mental distress in millions of patients worldwide, increasing socioeconomic burden and negatively affecting patient quality of life. The most common type of central demyelination disease is multiple sclerosis (MS), which remains an unsolved problem in the field of neurosciences with a mosaic of clinical manifestations and a long labyrinth of therapeutic approach.

Many factors cause the complicated etiological pattern of demyelinating diseases, some of which are innate and some of which are exogenous. Among the innate causes, genetic factors play a dominant role in the majority of cases of central demyelination [1] as well as in a considerable number of peripheral ones. Among a large number of exogenous agents are viral infections, dietary habits, smoking, obesity, physical or psychological trauma, latitudinal gradient and climate of a country, and ultraviolet light exposure. Genetic predispositions affecting autoimmune reactions, which are mostly mediated by T and B cells, play the most substantial role in the dramatic course and conclusion of the disease. Current therapeutic protocols are scheduled based on the autoimmune character of MS, attempting to control the activation of lymphocytes and the many cellular interactions characteristic of the disease [2].

In this volume, the authors analyze many aspects of demyelination from clinical, diagnostic, and therapeutic points of view. They describe the role of Schwann cells in the periphery and that of pericytes in the brain using experimental models, which offer the possibility of close observation and detailed study of the morphological alterations and pathogenetic mechanisms of demyelination and remyelination.

The multiform clinical manifestations of MS have a global character involving the physical, psychological, and mental aspects of the patients' life. The first chapter [3], discusses depression in patients with demyelination disease [4]. Rarely in serious cases, depression may be associated with suicidal ideation [5], whereas in the majority of cases it is related to anxiety, phobic phenomena, or even panic disorders that are proportional to the physical inability of the patients. On the contrary, some patients show emotional inertia, apathy, or absence of interest for the course of the disease. Many patients neglect environmental conditions and show behavioral changes, including euphoria [6], which might be attributed to the gradual degeneration of the frontal or prefrontal areas of the brain.

In Chapter 2, the authors discuss the non-pharmacological treatment of MS. The authors suggest that physiotherapy is a crucial and effective measure for increasing neuroplasticity and thus enabling the patient to retain functional independence. Physical education and exercises [7] may generally increase the concentration

of neurotrophic factors in the brain, enhancing synaptogenesis and improving the physical condition of patients. Among the various types of physical therapy, Judo seems to have beneficial effects in cases of relapsing-remitting (RR) MS [8], especially when incorporated at the initial stages of the disease, given that it may improve the development of proprioception, motor coordination, endurance, and muscle strength.

Chapter 3, [9], analyzes the activity of the Schwann cell, concluding that it plays a preponderant role in recovering nerve fibers after Wallerian degeneration, forming bands of Büngner, which guide the centrifugal propagation of axonal sprouts, reforming the myelin sheath and providing support for axonal outgrowth by the initiation of a reciprocal dialogue between axon and Schwan cell basal lamina by the plastic potentiality of Schwann cell [10]. Unfortunately, human Schwan cells have a limited in-time regenerative capacity and their contribution in axonal regeneration and remyelination gradually declines [11]. The authors underline that the understanding of the "extraordinary plasticity" of Schwann cells may inspire the introduction of novel therapeutic methods for the healing of peripheral neuropathies and traumatic nerve injuries.

However, all Schwan cells do not participate in the formation of the myelin sheath and the remyelination of damaged nerve fibers. Some of them, the so-called Remak fibers, are non-myelinated Schwann cells (NMSCs). Nevertheless, they have an important contribution in axonal maintenance and neuronal survival and are essential for the normal development and function of the peripheral nerves [12]. Remak fibers also play an important role in the modulation of pain sensitivity in peripheral sensory neuropathies. Chapter 4 describes in detail the different functions of Remak fibers according to their distribution in the nervous system [13]. Thus, the chapter describes their role as immune-competent cells [14] in the modulation of pain sensitivity in peripheral sensory neuropathies as well as in the formation and function of the neuromuscular junction. The authors' of this chapter conclude that a better understanding of the function of Remak fibers could lead to potential new treatment approaches to sensory neuropathies and even spinal muscular atrophy.

It is unanimously accepted that acute demyelinating polyradiculoneuropathy or Guillain Barré syndrome (GBS) is among the most serious conditions of peripheral demyelination. It is one of the main causes of flaccid paralysis in previously healthy individuals, particularly children [15]. In a considerable number of cases, respiratory infection is noticed to occur before the initiation of clinical phenomena of the disease. Chapter 5, describes an unusual case of recurrent GBS in a child who suffered from the disease in two successive episodes: from the acute inflammatory demyelinating variant in the first episode and from the acute axonal motor variant in the second one [16]. Both appeared following an episode of respiratory infection. The authors underline the value of early diagnosis based on the clinical estimation of the patient, in correlation with neurophysiological data, which should be important for the prompt therapeutic intervention of intravenous immunoglobulins (IVIGs) [17, 18].

Peripheral neuropathies are substantial causes of motor, sensory, and even autonomic disabilities with an unfavorable impact on quality of life. Among the broad etiopathological spectrum of these neuropathies, diabetic peripheral neuropathy

affects between 23% and 76% of the general population [19, 20]. Chapter 6 describes the various clinical and neuropathological types of diabetic neuropathies [21]. The authors emphasize the importance of the early clinical assessment of patients for proper management and treatment of the disease [22].

The vascular factor is an additional component in the broad pathogenetic background of central and peripheral demyelination. Anti-neutrophil cytoplasmic antibodies (ANCAs) may induce necrotizing vasculitis, which has polymorphic symptomatology including peripheral neuropathy in 50% of cases [23, 24]. In Chapter 7 [25] discusses the prevalence, clinical manifestations, prognosis, and treatment of peripheral neuropathies due to ANCAs, underlining that mononeuritis multiplex is the most common clinical form of peripheral neuropathy in antibodies-associated vasculitides (AAV), necessitating prompt treatment with corticosteroids and immunosuppressants [26].

The mechanical lesions of the peripheral nerves are not a rare phenomenon. Compression on peripheral nerves may provoke serious functional deficits, particularly whenever it occurs for a long time at certain points along the nerves' anatomical pathways [27]. In Chapter 8, [28] the authors discuss the many types of entrapment neuropathies concerning the upper extremities. The authors present a detailed schematic topographic analysis of the vulnerable points of the nerves along their course. In addition, they offer a precise description of the clinical signs of diagnostic significance in each one of the syndromes of entrapment neuropathies, highlighting the substantial role that anatomical variations, trauma, metabolic diseases, tumors, synovitis, and vitamin B6 deficiency play, among others, in their pathogenetic procedure [29].

The main doctrine in medicine based on the Hippocratic aphorism οφελέειν ή μη βλάπτειν is the alleviation of human suffering and the improvement of the quality of life of patients. For the realization of this doctrine, according to Galen, experimental research is essential for further understanding of the pathogenetic mechanisms of diseases and subsequent tracing of new proper and efficient therapeutic approaches. In the field of demyelinating diseases, the development of experimental models of demyelination and remyelination in vitro and in vivo is a necessity [30]. Given that MS has a dominant place in the spectrum of demyelinating disorders, several models of experimental encephalomyelitis have been introduced, approximating the clinical and neuropathological phenomena of the disease [31]. Many of those models, such as experimental autoimmune encephalomyelitis (EAE), toxic, viral, and transgenic models, are described in Chapter 9 [32], which emphasize the value of understanding MS via patient data.

Finally, Chapter 10 discusses the role of pericytes in demyelination and remyelination in an experimental model of MS [33]. It is known that pericytes participate in the functional neurovascular unit [34], being a substantial component in the development and maintenance of the stability of the blood–brain barrier (BBB). In addition, pericytes cooperate with other cells in the autoimmune reactions of the central nervous system (CNS), having the capacity to interact with oligodendrocytes and astrocytes and even to generate other cell lines. The chapter describes the ultrastructural characteristics of pericytes in EAE, concluding that novel therapeutic regimes that protect pericytes at the initial stages of demyelination may open promising new horizons in the treatment of MS.

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Section 1

Central Demyelination-Multiple Sclerosis

Chapter 1

Neuropsychiatric Symptoms in Demyelination Disorders

Any Docu Axelerad, Silviu Docu Axelerad and Alina Zorina Stroe

Abstract

Inflammatory demyelinating diseases are defined as being a miscellaneous group of disorders that develop as a consequence of an acute or chronic inflammatory process. The types of demyelinating disease with a high prevalence are multiple sclerosis, neuromyelitis optica and acute-disseminated encephalomyelitis. Patients with multiple sclerosis frequently experience depressive and anxiety symptoms including cognitive impairments. Depression is correlated with an unsatisfatory quality of life, having a conceivably important psychological impact on all the aspects of the patient's live, including less efficient coping mechanisms and a decreased compliance with disease-modifying drugs. As a general rule among population, depression in multiple sclerosis patients is regularly correlated with anxiety. The clinical importance of neuropsychiatric symptoms should not be neglected because multiple sclerosis patients are more prone to be affected in all the aspects of life, in view of the morbidity that these symptoms bring in patients with neurodegenerative diseases.

Keywords: neuropsychiatric symptoms, demyelination disorders, multiple sclerosis, depression, anxiety

1. Introduction

In the history of multiple sclerosis, noted as the first notation of the disease in the title of a neuropathological disorder was made by Charcot in 1868 [1].

In the evolution of multiple sclerosis, related to the diagnosis of the disease, a requirement is the apparition and subsequent demonstration of demyelinating lesions that are dispersed in time and location. In conjunction to the neurologic symptoms, the discovery of lesions through the magnetic resonance imaging are accordant with the diagnostic of multiple sclerosis [2, 3].

Further investigations include the evidence of the presence of oligoclonal bands located in the cerebrospinal fluid [4], and/or the discovery of pathological optical induced potentials (interruption with a conserved wave form) are suggested to acquire a proper diagnosis [5]. A monosymptomatic course of the disease could be existent in patients with multiple sclerosis, as well as an evolution including a classical relapsing remitting course of the disease or even a primary or secondary progressive disease.

The evolution of multiple sclerosis can be characterized by a constant degradation of symptoms from the neurological area, regardless of the lack of presence of

new MRI lesions and also a infrequent prevalence of lesions enhanced by contrast. The principal course of the disease for the most patients includes an onset represented by a relapsing remitting form of multiple sclerosis, with a subsequent evolution consisting of secondary progressive disease.

In the primary progressive form of multiple sclerosis, the evolution of the disease includes a continuous progression from since the commencement of the disease. Regarding the pathophysiological mechanism subsidiary to the progression of multiple sclerosis, the disruption of inflammatory nature of the blood–brain barrier is incriminated.

The underlying morphopathologic emblem of multiple sclerosis is the production of inflammation-related demyelinating lesions with variable lesions located at the axonal level, accompanied by deterioration as long as astrocytic gliosis.

In the course of the disease, including both early and late stages of multiple sclerosis, the lesions present in the following locations of the nervous system: neurons and the axonal level of the neurons, also synapses can be affected by the disease, the term used at large scale being represented by neurodegeneration [6, 7].

The axonal injuries and also the subsidiary loss have been proposed to represent a fundament to the extent of perpetual motor impairment in multiple sclerosis [8]. The acute injury with the location in axonal level is most enhanced in the active demyelinating injuries and can be recognized through immunohistochemistry.

Patients with MS commonly encounter through the evolution of the disease: signs and symptoms that are not especially a result of a relapse or the progressive stage, as fatigue, chronic pain, and urogenital dysfunction.

2. Depression in multiple sclerosis

Multiple sclerosis is correlated with a wide spectrum of neuropsychiatric disorders of which depression is the most frequent. Depression is a complex disorder taking into consideration, firstly, the symptom of madness and, secondly, the entire syndrome diagnosis of major depression.

The major depression syndrome was characterized by the American Psychiatric Association being a selection that includes nine signs and symptoms with the nominalization of five or more that are required be positive for minimum 2 weeks as a sequence for the positive diagnosis.

The symptomatology contains depressed disposition during the majority of the day, a disappearance of enthusiasm or enjoyment concerning occupations that consisted as pleasant previously, modifications in appetite related to weight loss or weight gain, insomnia or hypersomnia, a reduction or an increase in psychomotricity, agitation or lag, fatigue, impressions of uselessness or improper and exaggerated culpability, a decrease in the ability to concentrate, and persisting thoughts related to death.

For the medical health personal that is in relation with MS patients, the presented description can represent a possible issue taking into consideration the particularity of the symptoms that represent the base of depression's diagnosis that can further be induced by multiple sclerosis. The most occurring coincidental symptoms are those of fatigue, decreased concentration, and impairments related to sleep.

3. Quality of life

Depression prevalence in MS patients is correlated with a decrease in the quality of life regardless of the neurological or related to function deficits in correlation

with MS [9]. In a study by Carta et al. [10] was concluded that patients with MS and a subsequent chronic affection mood disorder present significantly decreased results on the SF-12 (an assessing instrument of quality of life) in comparison with MS patients wich do not present a history of mood impairments. In a study by Wang et al. [11] in which was assessed the MSQOL-54 score in multiple sclerosis patients, the participants that presented depression in antecedents, regardless of the state of their mood in the examination, provided significantly decreased MSQOL-54 averages in relation to energy, mental health, cognitive capacity and general quality of life.

4. Depression and cognition

In relation with the cognitive status, generally 40–70% of MS patients will present impairments in correlation with the disease type. Studies in the literature have concluded that clinically significant depression could conduce to a even more visible impairment in a patient's cognitive capacities. Studies by Arnett et al. [12–14], revealed that depression can affect in a negative way the working memory, especially the executive component. The conclusions exposed before suggest the probability that compensating the emotional disorders as depression have the possibility of influencing in a beneficial way the cognitive capacity in a multiple sclerosis patient, this theory was not demonstrated yet.

5. Adherence to disease-modifying drugs

Studies from literature have found a connection between the decreases in compliance for multiple sclerosis patients regarding to disease-modifying drugs [15–17]. In a study by Bruce et al. was demonstrated that MS patients which present an existing emotional disorder or anxiety disorder are approximately five times less probable to comply with disease-modifying therapy in comparison with MS patients that do not present psychiatric diagnosis positive [15]. A more favorable adheration in disease-modifying drugs was reported in patients with multiple sclerosis and secondary depression which received antidepressant therapy.

6. Suicidal risks

A third proportion of the MS patients experience suicidal ideation [18]. The predisposal factors are represented by: major depression episode, the level of severity of the depression, social detachment, and usage of alcohol and substances [19]. Suicidal thoughts and ideation represent risk cause for a suicide pursue. Studies related to patients with MS from the scandinavian region conclude that the mentioned patients are twice as inclined to attempt suicide compared to healthy subjects in the population [20–22].

Pujol et al. [23] studied the correlation between the depressive symptoms and cerebral dysfunction and concluded that hyperintense lesions with the location of left arcuate fasciculus were associated with Beck Depression Inventory scores. Other studies on the matter pointed out that lesion volume was associated with depressive symptoms but also stated that gray matter atrophy could represent a more powerful prognosticator of depression than lesion volume [24].

Feinstein et al. [25] used structural MRI on patients with multiple sclerosis and subsequent depression in comparison with patients which only presented multiple

sclerosis who were equal in terms of age, and duration of the disease's course, general disability and cognitive functioning. The conclusions were that MS patients with depression showed more hyperintense and hypointense lesions in the left medial lower frontal regions, as well as decreasing gray matter volume in the anterior left. Further analysis showed that these two factors predicted 42% of the probability variance to be diagnosed with depression [25].

Taking into account the presence of anomalies in the structure and also the dysfunctions that are constituents of; in patients with depression without neurological disease and their associated patterns of depression, the question arises as to the extent to which imaging results from patients with MDD bring us information about our understanding and determination of depression in MS.

A common variable of the existing work on depression is the hyperactivity of the limbic-prefrontal circuits that influences attention to negative stimuli, which when correlated with dysfunctional prefrontal regions involved in the executive control, can result in a prejudice of negative emotions or environmental stimuli without the necessary means to resolve or rethink the situation. The problem presented above is in connection with cognitive patterns of depression insisting on the role of dysfunctional cognitive schemes.

Considering the amount of atrophy that may be underlying MS, it is likely that localized atrophy in the prefrontal white and gray matter will help maintain depression through its negative role on emotional regulation. Although considering the fact that a small number of studies on the quantification of depression in MS through neuroimaging revealed localized atrophy primarily in gray and white prefrontal substances that partially overlaps with those areas found to be atrophied and/or have low activation of emotional stimuli.

Furthermore, there has been ample evidence that patients with MS have dysfunction in the course of their disease. Prefrontal activation as a response to cognitive control tasks such as working memory tasks. In this way, it is quite likely that decreases in prefrontal volume have a negative effect on the regulation of emotional emotions and the use of cognitive reassessments in MS patients [26, 27].

Moreover, monitoring the poor evolution of these networks, along with the evolution of the disease, as well as monitoring changes in the brain to the diversity of depressive symptoms, especially on responsibility for variable situations and poor emotional regulation, will be useful to successfully describe this neuropsychological presentation of a disease with a complex clinical evolution.

Summing up, it is shown that functional neural networks related to depression in the general psychiatric population have partially the same brain location as current findings of neuroimaging in MS. However, future investigations are needed to find clearer connections between depressive symptoms and specific structural abnormalities are essential, especially given the heterogeneity of atrophy and lesions in MS.

7. Anxiety and multiple sclerosis

In accordance with the standards defined by the American Psychological Association, anxiety represents "an emotion characterized by feelings of tension, worried thoughts, and physical changes like increased blood pressure" presenting as originator the anticipation of forthcoming warning or a motivational disagreement [28]. Anxiety is defined as a sentimental condition represented by unconcerned rational – implying thoughts of concerned predictions, physiological- implying corporeal invigorating, and behavioral elements [29].

The differentiation among anxiety and fear, as the latter represents the emotional feed-back in case of prompt warning, even though fear and anxiety are closely connected [30]. Furthermore, fear and anxiety are able to be differentiated using the support of duration, transitory center of attraction, warning particularity, and stimulated course: Taking into consideration that the sense of fear is experienced acute, emphasized in the present tense, and aimed to a particular warning, with the purpose of avoidance, anxiety is present in an extended period beyond particular warnings.

Subsequent to danger, fear and anxiety stimulate a concatenation of flexible practice with the scope of decreasing the disagreeable corporeal reaction in order to subdue the factual warning or settle the latent disagreement. Physiological type of anxiety and fear are extensively adaptive, as their effect is the acquisition of reserves with the scope of coping with a factual warning. Furthermore, extending anxiety is deliberately defective, and depending of its presentations, it might be a specific component of clinical diseases, as it has the effect of endangering the physiology and quality of life of the individual. Furthermore, pathological anxiety levels, in addition to the latter, materializes in the form of symptomatology as taking part of psychiatric diseases, specific to clinical depression.

Anxiety affections evolve in a matter of possessing a quantity of biological and social determinants being partly responsible of the apparition and evolution of the symptomatology. On this matter, malfunctional anxiety can be acquired from the social or familial habitat, in the existence of a biological inclination [30], or it can be the consequence of adverse life circumstance being acquired trauma. In the study of Bruce et al. [15], on the theme of connections related to worry and anxiety in MS patients has revealed the fact that nevertheless, the significant correlance with anxiety, worry can be revealed as a unique and independent element.

Even though anxiety related diseases are frequently diagnosed in multiple sclerosis patients, this pathology is in some cases neglected and investigated more superficial in comparison with other representatives of neuropsychiatric disorders such as depression. However, the occurrence of anxiety disorders in patients with MS is statistically more important in comparison with the general population. In a study by Korostil et al. [31], was demonstrated that lifetime rates of anxiety in patients with multiple sclerosis are more increased in comparison with the rates of anxiety in chronic medical illnesses. Accordingly, a more wide investigation on the theme of anxiety disorders in multiple sclerosis pathology is recommended.

Even though a significant number of studies investigated anxiety in MS, a large proportion of the literature on the subject is counterfeit by assorted constraints, being the absence of clinical interviews, which are essential toward to systematize a clinical interpretation. Certainly, even if educational, the preponderance of the studies on the theme of emotional impairments in MS specially commit on self-report measurement instruments as questionnaires and scales for the determination of clinically significant anxiety with some exceptions.

In a study by Galeazzi et al. [32], was concluded that the prevalence of anxiety consisted of 36% of a quantity of 50 patients with MS with the usage of the instrument: the Structured Clinical Interview for DSM-IV disorders (SCID-IV). Furthermore, as in the study of Galeazzi et al. [32], in a study by Shabani et al. [33], the conclusions revealed that MS patients were more suitable for the diagnostic of obsessive–compulsive disorder than anxiety. Also, in a study by Korostil et al. [31], using the scales: Structured Clinical Interview for DSM-IV disorders and Hamilton Anxiety Depression Scale, was concluded a lifetime prevalence of anxiety disorders of 35.7% in the sample of the MS patients. Among of the conclusions of the studies, was also revealed that anxiety disorders were widely underdiagnosed between multiple

sclerosis patiens, hence limiting the opportunity of providing the essential treatment in the targeted disease.

Various elements should be considered in the case of referring to the clinical manifestations of anxiety in MS. Regarding this matter, a constant problem in the clinical objectivation of psychiatric impairments, being anxiety and depression is represented by the symptom projection along with somatic symptomatology of MS. As it is the case, various somatic elements of symptomatology related to anxiety being restlessness, vertigo, episodes of loss of consciousness, and leg unsteadiness that can be often prevalent amidst the corporeal symptomatology of MS. In the matter of the investigations of the issue of depression, the literature conduced on the theme of symptom overlaying among anxiety and MS is insufficient [34].

The overlaying of the symptomatology among anxiety and MS was further investigated and emphasized in a retrospective study by Carmonsino et al. [35]. In the same study, the conclusions revealed the presence of psychiatric diagnoses in 63 MS patients in which the primary objective clinical investigation implied the presence of a primary psychiatric etiology for the patients' symptomatology. In the same study, a major preponderance of 92% of MS patients completed the diagnostic criteria for one or more psychiatric diseases containing personality, somatic, and anxiety impairments. Therefore, clinicians are advised to present large amounts of deliberation in the attempts of determination of psychiatric disorders generating neurological-like and also nonspecific symptomatology - likely anxiety, and also, special caution regarding the evaluation of anxiety only using the screening instruments, as this symptom overlie might increase the scale records and demand additional investigation using a clinical consult.

In the study of Korostil et al. [31], investigated the occurrence of certain anxiety disorders using as instrument a clinical consult based on the interview method concluded that generalized anxiety disorder is the most frequent in the cohort of MS patients. Generalized anxiety disorder is represented by unmanageable concern followed by various physical symptomatology including: cephalalgia, vomiting sensation, muscle tightness, and swallowing impairments.

The presence of generalized concern and health related anxiety in MS patients has been emphasized in several studies, and and this fact is not surpring, considering the nature of the complex demyelinating disease [36–38].

In a study by Janssens et al. [39], a correlation was made among the understanding of evolution risk and anxiety in the case of patients with multiple sclerosis. On this matter, the patients who considered that they would use a wheelchair in the further 2 years experienced more elevated levels of anxiety and depression. Interestingly, patients had the tendance to exaggerate in estimation their short-term risk of using wheelchair.

In a study performed by Jopson et al. [40], was revealed the correlation among multiple sclerosis features and anxiety, explained with the evidence that the patient's inclination to consider inconstant and unclassifiable symptoms as cephalalgia and aching to MS might cause anxiety among the patients in the cases they consider the mentioned symptomatology as causative for progression in multiple sclerosis.

Exaggerated anxiety and concern regarding health develops in more necessity for medical attendance [41] and greater corporeal impairments [42]. Kehler et al. [38], discovered that MS patients which present increased anxiety related to health are inclined to a lowed degree to practice issue-focused coping methods, favoring emotional concentration and familial assistance as principal coping method. The cases of patients in cause also revealed that increased standards of health related anxiety propose and encounter higher disability and also generalized anxiety disorder. The former conclusions are emphasized with the ideas revealed from the

study supervised by Feinstein et al. [43], in which was revealed that the presence of anxiety and depression in patients with MS culminate in greater corporeal health related concerns and familial and group malfunctions. Among the conclusions of the study was also the theory that the liabilities of self-harm and suicidal judgment in patients with MS are the consequence of existence of both anxiety and depression and not isolated depression.

Studies on the matter of the consequences of exacerbations on the emotional state showed that the aggravation in the evolution of the disease, heightens the level of emotional distress when assessed with the remission phase [44–46].

Interestingly, MS patients often state that in the extent prior to the commencement of the symptomatology, subsequent diagnosed as being the onset of MS, or anteriorly to the exacerbations, significant disturbing circumstances have occurred. In some cases, between the reports of the patients were encountered bizarre, abnormal subjective sensations and perceptions prior to the relapse symptomatology.

Methodical conclusions of several studies have revealed that aggravating occurrences are correlated with a higher frequency of exacerbation, not taking into consideration the infectious etiologies and psychosocial elements as unfavorable familiar and social circumstances in relation with anxiety which are correlated with MS commencement [47–51].

The possible existence of anxiety, including another emotional related symptomatology, with psychological impairments in multiple sclerosis drew attention to the concern of different investigators. Dysfunction of various cognitive activities modifies an important part of the evolution of MS patients and it is accordingly appropriate to analyze all the potential causes.

Anxiety stages and anxiety related diseases are more prevalent in MS patients compared with the general population; with an undesirable elevation in anxiety which is described in the literature as being more prevalent compared with depression, in the papers that examined the same sample of patients.

In the study by Carta et al. [10], was concluded that multiple sclerosis is correlated with a unsatisfactory quality of life in comparison with psychiatric diagnosis of bipolar disorders, major depression, or eating disorder or to various neurological diseases being Wilson's disease. In one study that used as sample patients with MS, the quality of life was more affected in the cases of comorbidity consisting of bipolar disorders, compared with the comorbid represented by major depressive disorders [10].

Respecting the pattern prevalent in the general population, depression in MS patients is frequently correlated with anxiety. The clinical significance of this type of morbidity should be taken into consideration because MS patients that experience twain anxiety and depression are more prevalent to present a high frequency of thoughts related to self-harm, more important somatic discontents, and be even more socially impaired in comparison with MS patients with depression or anxiety singularly [43, 52].

Regarding the symptomatology the frequency is higher in anxiety than depression as a solitary symptom, and the occurrence of generalized anxiety, panic disorders, obsessive–compulsive disorder, and social phobia are significantly more frequently encountered in MS patients compared to the general population [53].

In a study that included 115,071 adult Canadians, the 12-month prevalence of depression in MS subjects was increased twain in healthy individuals and in individual that presented chronic medical diseases [54]. The most significant prevalence of depression was reported in individuals with the age between 18 and 45 years.

Other studies revealed the high prevalence of depression and anxiety among the multiple sclerosis patients with the presence of furthermore debilitating symptomatology [55–57]. A study using administrative data from Canada revealed that

the risk of psychiatric disorders such as: depression, anxiety, and bipolar disorders is more prevalent in multiple sclerosis patients in comparison with the general population.

There has not been established a correlation between the diagnosis of depression and the characteristics of the disease, furthermore, the correlation with physical disability is uncertain [54, 58]. The ambiguity is presented in relation with the disease duration [59].

The conclusions presented could have the explanation of the ambiguity as a result of the ambiguity of the disease, with multiple different presentations. In the acceptation of the facts stated before is the fact that patients which present the similar disease duration can possess a definitively contrasting relapse rate or disease evolution. Furthermore, the stage of of physical impairment could be decided by a combination of cerebral and spinal affection, twain presenting a conceivably distinctive mood related consequence.

The presence of depression is correlated with a deficient quality of life, significant cognitive impairment, a high rate of suicidal thoughts, and a decreased compliance with disease-modifying drugs.

8. Bipolar disorders in multiple sclerosis

Bipolar disorders and broadly mood related disorders were considered as being a primordial symptom of MS [60], as the performing of mood symptomatology was reported to be initiated previously of the manifestation of the neurological features [61].

Appealing and adjacent connections that associate energy metabolism, inflammation, and demyelination were prevalent in multiple sclerosis. Furthermore, the results of oxidative stress at the oligodendrocyte level can be located between down manifestation of oligodendrocyte genes – as noticed in psychiatric diseases and in bipolar disorders specifically – to cell destruction and brain impairments emblematic of MS [62].

The susceptibility for bipolar disorders might appear as a result of the dysfunction of the brain courses controlling emotions, motor behavior, and pleasure [63, 64].

9. Euphoria in multiple sclerosis

The definition of euphoria includes the description of a constant extreme happiness and happiness, an inadequate animation, or a absence of interest in the concerns of repercussion of the disease. This disorder arises as a sequence of personality related disorders and it is not defined as a disposition related disorder. Euphoria represents a distinct disorder compared with mania. This disorder is correlated with the apparition of the following features: infantilism, spontaneousness, emotional impairments, anger attacks, and absence of sympathy. In recent studies from literature, the occurrence of euphoria was reported to be approximately 15% in patients with multiple sclerosis.

In a study by Diaz-Olavarietta et al. [65], which included 44 patients as MS group and 25 healthy patients as control group, the prevalence of euphoria was reported to be present in 13% of the patients presenting multiple sclerosis, meanwhile the control group was euphoria-free.

In a study conducted by Fishman et al. [66], which included 75 patients with multiple sclerosis, was reported a presence of euphoria in 7% of the multiple

sclerosis patients, compared with the healthy subjects which did not present any of the symptoms associated with euphoria.

Euphoria is neuroimagistically correlated with the rigor of the amount T2 lesions and the degeneration of gray and white matter [67].

10. Conclusions

There is conclusive data relating depression manifested clinically in a consequential manner in MS patients to a variety of unfavorable results in relation with occupations of daily living. Due to the particularly wide and varied implications of multiple sclerosis, it is important that the disciplinary team of physicians treating patients with this condition be alert to any changes in symptoms and aware of the increased prevalence of neuro-psychological disorders in the course of the disease.

This point is reinforced by studies showing the effectiveness of treatments for patients with multiple sclerosis and depression. Successful treatment will not only decrease MS-related morbidity; but it also has the potential to reduce suicide-related mortality.

Related to the presence of associated symptoms, depression is the most common psychiatric complaint in patients with multiple sclerosis, and this conceives 25 to 50% of patients during the course of the disease, which is from two to five times higher compared to the prevalence rate in the general population. The cause of such a frequent occurrence of depression in patients with MS becomes more evident in the light of pathophysiology brain changes, and psychosocial changes are likely to be important in the course of the disease.

Psychiatric disorders have a significant frequency in multiple sclerosis cohort of patients. The risk of suicide is specifically considerable in the initially part of the disease's evolution. Anxiety is prevalent in multiple sclerosis and is the most influential prognosticator of the manifestation of depression. Major depressive disorder is inadequately diagnosed and treated. Behavioral impairments are more prevalent in comparison with severe psychiatric diseases and appear apparently subsequent to cognitive dysfunction. Addictions might be not diagnosed appropriately.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

None.

Appendices and nomenclature

MS	multiple sclerosis.
MRI	magnetic resonance imaging.

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Chapter 2

Role of Physiotherapy and Practice of Judo as an Alternative Method of Treatment in Multiple Sclerosis

Katarzyna Wiszniewska

Abstract

Multiple sclerosis is a chronic inflammatory-demyelinating disease, which is most frequently diagnosed in young adults. Physiotherapy, mainly kinesiotherapy, plays an important role in supporting the therapeutic process. Research shows that physical activity may delay the progression of the disease and influence its course. Physical exercise can stimulate the secretion of neurotrophic factors that induce neuroplastic processes within the central nervous system, thus contributing to the recovery of motor and cognitive functions. The young age of the patients makes it difficult for them to accept the need to attend rehabilitation sessions on a regular basis. There is a possibility to use alternative forms of rehabilitation based on sports disciplines or other physical activities. A pilot study was conducted, in which judo training was incorporated into the rehabilitation program for MS patients. The benefits of this sport include: development of proprioception, motor coordination, endurance and muscle strength. The study showed a reduction in the symptoms of MS in the participants.

Keywords: multiple sclerosis, physiotherapy, physical activity, alternative rehabilitation, judo, disability

1. Introduction

Multiple sclerosis (MS) as a disease: acquired in young adulthood, chronic and of undetermined etiology is difficult to accept by the patient. Comprehensive therapy based on pharmacological treatment combined with regular rehabilitation is required. Physiotherapy is aimed at maintaining the psychomotor performance of the patient for as long as possible. There are ongoing studies and discussions on determining to what extent the physiotherapy directly affects the regeneration of nervous tissue, and to what extent its satisfactory effects are related solely to the increase in the level of physical activity [1, 2]. A comprehensive rehabilitation program should motivate the patient to live in a dignified and enjoyable way. The pilot studies show that the patients enjoy alternative forms of physiotherapy that influence the locomotor system and engage in them on a regular basis. What is more, this kind of activities helps patients to develop various interests and improves their social relations [3]. Given the high specificity of MS, the physiotherapy should be fully integrated into the treatment program and adapted to the individual needs of the patients, as well as their capabilities and stage of the disease [1, 2]. The following chapter presents recommendations

for alternative forms of rehabilitation used in the comprehensive treatment for multiple sclerosis, such as judo, tai-chi or kick boxing.

2. Role of physiotherapy in the treatment of multiple sclerosis

The most effective non-pharmacological treatment for patients diagnosed with multiple sclerosis include physiotherapy, symptomatic therapy and psychotherapy [4]. The key of the effectiveness of the therapy lays in its all-encompassing character, that is, the cooperation between a doctor, physiotherapist, nurse, social worker, occupational therapist as well as psychologist. In case of some patients, it is not necessary to involve all the specialists listed above. Starting from the diagnosis of the disease and through its development, the patient's situation should be analyzed on an ongoing basis and based on that, they should be under observation of particular specialists. Close cooperation between the physician and the physiotherapist seems to be indispensable in every case of multiple sclerosis [5]. Regular physiotherapy allows patients to maintain independence for longer. The positive effects of the physiotherapy are possible due to the neuroplasticity of the brain. Neuroimaging and electrophysiological examinations show spontaneous and physiotherapy induced changes in the nervous system [6]. Correlation between physical exercise and recovery of motor and cognitive functions in patients is being studied. The studies largely focus on the role of cytokines and neurotrophic factors in these processes, in particular brain-derived neurotrophic factor (BDNF). Increased BDNF levels are observed after regular physical exercise. Brain-derived neurotrophic factor (BDNF) is one of the nerve growth factors. It enhances neuronal regeneration, promotes the survival or nerve cells and influences Schwann cells. Data obtained in several studies show relations between the increased levels of neurotrophins observed after regular physical activity and the induction of neuroplasticity, as well as the recovery of motor and cognitive functions. According to some sources, the plasma cytokine and neurotrophins concentration depends mainly on the type of exercise (light/intense) and not on engaging in a physical activity itself [7, 8]. It is emphasized that patients with multiple sclerosis can tolerate longer training sessions of high and rapidly increasing intensity, which allows them to make a more noticeable progress in less time. In patients with multiple sclerosis, endurance physical activity, in particular short and intense series of exercises, significantly increases cardiorespiratory fitness and leads to an increase in the secretion of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Sensory symptoms worsening may be observed after kinesiotherapy. However, this is a temporary effect that resolves within half an hour after the exercise session [7].

It is difficult to identify a clear cause of disability in patients with multiple sclerosis. It seems that the patient's fitness is reduced not only as a result of the progression of the disease. It may also be a consequence of reduced physical activity in MS patients compared to healthy people. Patients with multiple sclerosis, due to lack of regularity in undertaking physical activity, show a reduction in both the maximum aerobic capacity (maximal oxygen consumption) and muscle strength, which additionally translates into impaired functional capacity and reduced quality of life. The physiological profile of these patients may be a consequence of the irreversible effects of the disease as well as of the inactive lifestyle [4, 9]. The effectiveness of the treatment depends on the stage of the disease and the effects of secondary lack of physical activity. It is not clear to what extent the individual impairments can be reversed, as well as to what extent physiotherapy can boost the remyelination of the nervous system. However, kinesiotherapy carried out on a regular basis can certainly contribute to the improvement of the patient's general condition by reducing

the effects of lack of any physical activity. Therefore, rehabilitation in MS remains the main non-pharmacological strategy that allows to reduce disability and maintain patient's functionality [9].

According to the National Multiple Sclerosis Society based in the US, rehabilitation in MS helps patients to achieve and maintain their maximum physical, psychological, social and professional potential, as well as quality of life in relation to the disease, environment and their life goals. Achieving and maintaining an optimal condition is necessary to accept a life with a chronic illness [9]. Exercising particular functions, improving muscular strength and working on proprioception facilitates the patients' everyday life. In case of patients diagnosed with MS, mental attitude is of an extreme importance. When preparing a rehabilitation and physiotherapy program, attention should be paid to the patients' mental state, as well as to their level of motivation to exercise on a regular basis. The aim of physiotherapy, in addition to the physical aspects, is to improve patient's mental condition. A properly selected program will allow the patient to achieve the intended results. Thanks to such an approach and action, patients gain confidence in themselves and their movements and it is easier for them to accept the disease together with its consequences, while finding their place in the society [1, 4, 7]. The rehabilitation should focus on restoring the functions lost by the patient or properly controlling the compensation processes in order to use the patient's adaptive abilities in the most effective way [5].

Generally speaking, in the case of MS patients, rehabilitation should begin with educating the patients and their relatives. It is important to explain the need for regular rehabilitation and its correlation with the pharmacological treatment. It should be noted that the physiotherapist together with the patient sets rehabilitation goals at each stage of the disease. Education is more effective at the early stages of the disease, because the patient shows lower degree of disability and can be taught the correct pattern of performing particular movements in an effective way, which may be useful in the later stages of MS [10, 11]. Then, the so-called symptomatic and task rehabilitation is introduced. It consists of teaching the patients specific functions that may facilitate their everyday life [4]. The detailed plan of the physiotherapy depends on the dysfunctions presented by the patient, the course of the disease and the patients' needs (including their attitude). Structured therapy should also include the patient's individual work at home [10].

Each patient may show different symptoms, which may hinder their everyday life to a varying degree. Physiotherapy aims at choosing a method that can treat several ailments at the same time [11]. Depending on the patient's needs, the emphasis is put on different types of exercise: exercises that increase muscle strength, improve proprioception and coordination or the aerobic exercises. A combination of various types of training is used in order to obtain better results. For instance, a combination of endurance and resistance training improves mobility, balance and coordination [4, 12]. Due to the early age of the diagnosis, the progressive nature of the disease, symptoms that hinder normal functioning and are often embarrassing and may contribute to depression, alternative forms of physical rehabilitation are increasingly being considered. Many types of physical activity can be adapted for therapeutic purposes. Therapy derived from a specific type of sport has a positive effect on the level of motivation to undertake the effort as well as the patient's well-being and self-esteem. This approach allows patients to feel that their goal is not limited to preventing the effects of the disease – the dysfunctions they present–– but it is an opportunity to learn new skills, develop new interests or maintain the previous ones. In particular, at the initial stages of MS, it is beneficial to introduce unconventional forms of rehabilitation, which have therapeutic effects, but at the same time may become an alternative way of spending free time. It may support the process of accepting progressing disability. A person who

notices his or her limitations often tends to isolate oneself from society and shows a fear of learning something new. The use of unconventional methods of rehabilitation is aimed at: helping the patient overcome fear, building self-confidence, motivating them to spend time with other people, and encouraging them to adopt a more open attitude, thus facilitating a conversation about their disability. Different activities can be used for therapeutic purposes, including: aerobic training, cycling, judo, tai chi, kickboxing, bicycle ergometer, yoga, aqua spinning and other water exercises [4, 7, 12, 13].

3. Judo: an alternative form of physiotherapy in the treatment of multiple sclerosis

An experiment was conducted, in which a program of physiotherapy for patients with relapsing–remitting (RR) multiple sclerosis was developed on the basis of judo elements. The study involved 4 women aged from 32 to 49 years who had been suffering from MS for several years (from 3 to 7 years). Before being qualified into the study, their physical activity was varied. Prior to the beginning of the study, the patients did not undergo any supervised physiotherapy. In the functional assessment, they presented different levels. However, all of them were able to move independently. They reported the following problems related to the disease: urinary incontinence, chronic fatigue, balance disorders and sensory disturbances. In addition, 3 respondents reported a sense of social isolation despite being active professionally. None of the women had practiced a sport like judo before. Unconventional therapy involving judo elements lasted for 8 weeks. All patients fully executed the plan they were provided with. The women participated in judo training supervised by a physiotherapist twice a week, in 45-minutes sessions and performed exercises at home twice a week, in 20-minutes sessions. The number of classes and their duration were determined based on the guidelines of physical activity for patients with MS developed by the Canadian Society for Exercise Physiology, which received a recommendation from the Multiple Sclerosis Society of Canada [14]. The participants exercised barefoot in sportswear in a room with a relatively low temperature (around 15°C). The program of classes included the following: learning about history and philosophy of the discipline, demonstration of throws and combat by professional sportsmen, coordination exercises (alternating arm circles, etc.), learning falling techniques from various positions (*ukemi*), ways of moving on the mat, body turns and body rotations, special judo exercises aimed at strengthening the stabilizing muscles of the torso, the so-called central stabilizers (moving: sitting straight forward and backward, lying back and forward, lying backwards with alternate right and left bends of the body, in a standing position with bent lower limbs, taut torso and bent upper limbs, etc.), learning 3 basic holds (*osaekomi - waza*) and getting out of them, performing individual throwing techniques without a partner (*tandoku - renshu*), responding to sound and visual signals, exercises and games aimed at throwing the partner (*uke*) off balance (including: pulling/pushing an *obi* with one's hands, pulling with the left upper limb and thrusting with the right, and vice versa, pushing the partner while approaching him), taking defensive positions on the ground (*ne - waza*) and trying to maintain them, training fights on the ground (*randori ne - waza*), adjusting one's own movements to the partner's movements, moving around the mat with your partner, entering different techniques with the partner (*uchi - komi*) in a spot or in movement, *tandoku - renshu* with closed eyes and overcoming the partner's resistance. Each class began with warm-up exercises and ended with breathing and relaxation techniques on the basis of post-isometric muscle self-relaxation. The tasks to be performed at home correlated

with the current stage of the rehabilitation program. Therefore, the plan included: coordination exercises (alternating forward and backward arms rotations), stabilization exercises, the so-called CORE (starting positions: point kneeling and lying on the back), falling on the mattress/bed, *tandoku - renshu* (also outdoor), simulation of exits from holds without a partner and breathing and relaxation exercises.

Prior to the start of the rehabilitation program and at the end of the program, patients completed the Multiple Sclerosis Impact Scale (MSIS - 29) questionnaire. The results showed that in the assessment of patients, the physiotherapy contributed to the decrease in the degree of their disability, both physically and mentally. Each of the women, after eight weeks of judo practice, in response to the questions contained in MSIS-29, emphasized that the intensity of the dominant and most bothersome symptoms significantly decreased compared to the baseline assessment. This proves that judo classes had a positive effect on the functional status of the patients (**Table 1**).

Before and after the study, the following tests were also performed: Lovett (for muscles: rectus femoris, biceps femoris, rectus abdominius, deltoideus), Time Walking (10mTW), Functional Reach Test and body posture assessment. The comparison of the results showed an improvement in all the areas after the completion of the program. One of the patients initially showed significant lack of balance that negatively affected her stability and movement. Prior to the physiotherapy, her gait was abnormal: small steps, slightly spastic and shaky, with wider base. She also reported fear of falls, which occurred regularly. Each time, she feared possible injury and a sore body. After therapy, however, she showed a more stable body posture when moving. Her gait improved and was closer to physiological one. In addition, the feeling of fear of uncontrolled falls decreased significantly, as during therapy she learned how to fall in a way that cushioned her fall to the ground.

All the patients who participated in the study stressed that they gained self-confidence, felt less muscle tension, acquired control and inner peace, while their well-being improved. They reported much higher levels of concentration and observed that they were able to perform daily activities faster than before. In addition, they estimated that the level of depression they felt decreased within these two months.

On the basis of the pilot studies, the following conclusions can be drawn:

1. Practicing judo by people with multiple sclerosis improves all motor skills (speed, strength, endurance, coordination). Judo exercises allow to reduce the fatigue. Based on the results obtained in this study, it cannot be clearly stated whether the therapy had a direct effect on the chronic fatigue or only increased the level of tolerance for physical efforts, thus indirectly reducing this symptom.

Patient	MSIS-29 before starting the judo program points/%	MSIS -29 after completion of the judo program points/%
1.	63/43%	48/33%
2.	92/63%	60/41%
3.	67/46%	45/31%
4.	98/68%	58/40%

Points - number of points obtained, % - number of points obtained x 100% /maximum number of points (maximum number of points = 145).

Table 1.
Analysis of the MSIS -29 questionnaire before and after the 8-week judo program.

2. MS patients, who performed specialized judo exercises, show improvement in term of balance, because those exercises require a constant activation of a large number of joints (both in the lower and upper extremities), which causes stimulation of deep sensation receptors. Constant stimulation of the muscle of the abdomen, pelvis and lumbar spine promotes maintaining a stable body posture.

3. Specialized judo exercises increase muscle strength within the abdominal muscles and pelvic floor, thus reducing urinary incontinence.

4. Judo is a contact sport. During the practice, frequent stimulation of mechanoreceptors in the skin occurs, especially when the exercising person is dressed in sportswear of normal thickness such as shorts and a T-Shirt. This can have a direct effect on improving surface and deep sensation. Pressure and precise touch (in judo they are continuously triggered by the embrace/compression of the body to perform a given technique) are transmitted along the same pathways as information from proprioceptors. As a result, proprioception is also improved.

5. Acquiring the ability to fall safely results in: more stable body posture, more confident and determined gait, more complex movements and actions that the patient previously tended to avoid. It also reduces the risk of suffering mechanical trauma as a result of a fall.

6. Performing complex movements in an open kinematic chain (throwing techniques), which require high concentration, precision, correlation of two hemispheres and motor coordination, improves cognitive functions. It may suggest that judo can have indirect beneficial effect on the process of regeneration of neural tissue.

7. Conducting physiotherapy based on a specific sport contributes to increased motivation and conscientiousness during exercise.

8. Working on correcting the patient's impaired functions is easier if combined with acquiring new skills, such as learning judo techniques. The patient then participates in the training more willingly and consciously.

9. The patient's attitude to achieve a specific goal, in the form of learning to perform previously unknown activities, increases self-confidence, promotes better and more open interpersonal relations and has a positive effect on the patient's attitude.

10. The positive results obtained in this pilot study suggest that it may be worth conducting a study involving a larger population.

4. Why was judo selected for rehabilitation in MS?

Judo is a sport that develops all motor skills, that is, speed, strength, endurance and coordination. In addition, it promotes proprioception, as well as increases mobility in the joints and improves muscle stretching. The practice consists of making the opponent loose his or her balance while, at the same time, trying to control one's body posture in different planes. It is widely believed that

the main determinant of success in judo is the efficiency and effectiveness of the postural control system. Therefore, when performing different exercises, techniques (*nage - komi*) as well as free practice (*randori*) the participant learns to feel the body movements and the position of the opponent (*uke*) and use unstable and dynamic situations on his or her favor. Constant stimulation of mechanoreceptors and proprioceptors and the liberation of adequate tension of stabilizing muscles within the trunk occurs constantly in the participant's body. A correct correlation between the central nervous system and the locomotor system (musculoskeletal system) is very important. In addition, judo is trained barefoot. The feet have the control over the transmission of information received both from the outside (position on the ground) and from the inside (adopted position) [15, 16]. Superficial mechanoreceptors located on the plantar side of the foot provide the CNS with information on the position of the body in relation to the vertical reference, based on gravitational forces, load-bearing surface reaction forces and shear forces, which plays an important role in maintaining a stable vertical position [17, 18].

Making unexpected moves imposed by the opponents can have a beneficial effect on improving the movement coordination of judokas in unexpected situations. The training enables them to develop they sensorimotor adaptation that also influences the control of body posture in other situations. During the judo practice, the central nervous system – thanks to available sensory information as well as biomechanical constraints – controls the position of the center of gravity of the body in relation to the feet and creates posture patterns that allows to maintain balance in a given position. Improving postural control as a result of practicing judo seems to be a consequence of improving motor coordination (postural strategy), primarily based on somatosensory information received from one's body.

It is worth paying attention to learning falling techniques in the context of falling to the ground in a safely way. Maintaining control prevents injuries and reduces the discomfort during the fall. A fall is an unintended change in the body position, which consists of losing the balance when walking or performing other activities. As a result of the fall, a person unexpectedly finds oneself on the ground or other low-lying surface. The probability of injury to various tissues increases at the moment when the speed of the person who falls rapidly drops to zero, as a consequence of the collision with the ground. From the biomechanical point of view, a fall can be broken into four phases. **The first phase** of adaptation to the repositioning of the body occurs unconsciously. Reaction that occur in the upper part of the trunk create increased muscle tension. **In the second phase**, still in an unconscious way, vestibular system reacts stimulating the lower kinetic chain. **The third phase** occurs consciously and aims to protect the spine from injury. The person who falls bends the body, with the simultaneous reduction of cervical and lumbar lordosis and rounding of the back. **The fourth phase** consists of a rapid energy dissipation and a reduction in the reaction force of the ground by hitting the outer edge of the upper limb against the mat (**Figure 1**) [20].

Judo is among sports commonly practiced by people with intellectual and motor disabilities. It is one of the disciplines included in the Paralympic Games. This sport is practiced, among others, by: blind or visually impaired people, people with impaired hearing, Down's Syndrome and with Cerebral Palsy [18, 21–23]. Judo elements were also used in the physiotherapy of patients after stroke [24]. The positive effects of the alternative methods of rehabilitation (such as tai-chi, kickboxing and yoga) among MS patients, as well as the many benefits of judo and its high therapeutic effectiveness demonstrated in groups with disabilities was one of the reasons why practice of judo by MS patients was considered.

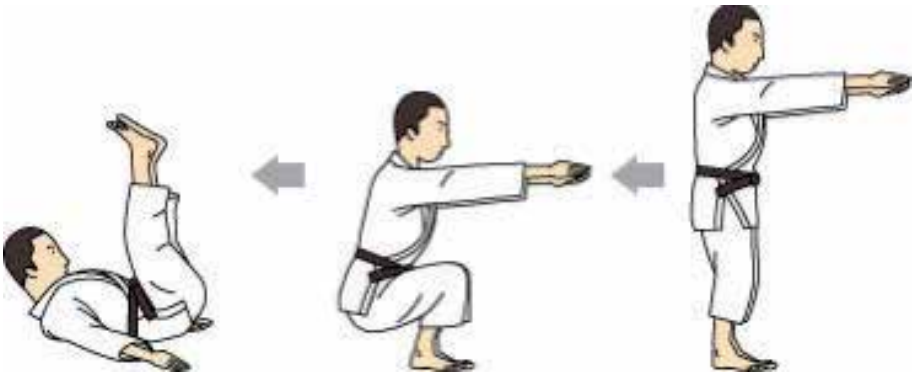

Figure 1.
Learning ukemi *[19]*.

5. Conclusions

Regular rehabilitation is very important for patients with multiple sclerosis. First of all, physical activity reduces the existing dysfunctions and allows to maintain the independence for longer. Development of the disability in MS patients can be caused not only by the progression of the disease but also by reduced physical activity compared to healthy people. It is suggested that rehabilitation may delay the progression of MS. Physical activity can stimulate changes in neuroplasticity of the brain. The role of cytokines and neurotrophic factors, in particular brain-derived neurotrophic factor (BDNF), in these processes is stressed.

The type of therapy undertaken and its effectiveness in eliminating the resulting dysfunctions depend on many factors, but above all on the stage of the disease, the effects of secondary physical inactivity and the patient's motivation. Kinesiotherapy conducted on a regular basis can help to improve the general condition of the patient, both physically and mentally.

Comprehensive rehabilitation should be introduced as soon as MS is diagnosed. Physiotherapy should begin with education, that is, explaining the patient the reason behind the regular physical activity and preparing him or her for the progressive nature of the disease. Most patients are diagnosed with MS at a young age and the correct patterns should be taught to them at the initial stage, as they may be useful when his or her condition deteriorates. When treating MS patients, it is important to bear in mind that they are losing functions that used to be natural to them. Therefore, alternative form of rehabilitations are worth considering. It is necessary to plan a therapeutic program in such a way that the patient, despite the prospect of the increasing number of dysfunctions, is willing in undertake physical activity. Physiotherapy cannot become a cause of mental suffering of the patient, resulting from the awareness of the progression of the disease. It is worth implementing a therapy based on the patient's previous interests or a method that requires the patient to learn new skills. Judo can be an attractive form of rehabilitation for patients with multiple sclerosis.

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Section 2

Peripheral Demyelination-Schwann Cells

Chapter 3

Schwann Cell Plasticity in Peripheral Nerve Regeneration after Injury

Emilia Manole, Alexandra Eugenia Bastian, Ana Maria Oproiu, Monica Teodora Neagu, Carolina Constantin and Gheorghita Isvoranu

Abstract

In the normal peripheral nervous system, Schwann cells (SCs) are present in two different states of differentiation: myelinating SCs that surround large-caliber axons, forming myelin sheath, and non-myelinating SCs that surround more small-caliber axons forming Remak bundles. Under pathological conditions (injury or inflammation), SCs, with a remarkable plasticity, undergo phenotypic transformations, downregulating the production of myelin proteins mRNAs, upregulating neurotrophic factors and cytokines, thus promoting the axonal regeneration. Dedifferentiated SCs activate the protein degradation, participating in the demyelination process and clearance of myelin debris; attract macrophages helping wound healing; proliferate to replace lost cells; guide axonal growth; and protect against secondary axonal damage. Thus, SC functions have a critical contribution to regeneration processes that occur in peripheral nerve after injury.

Keywords: Schwann cell plasticity, dedifferentiated Schwann cells, peripheral nerve regeneration, myelin recovery

1. Introduction

Schwann cells (SCs) are glial cells present in the peripheral nerve system (PNS). The name was given in honor of the German scientist Theodore Schwann, who discovered them in the nineteenth century [1] although they were not the main subject of his research. At that time it was thought that this type of cells is very complex and that the cells merge to supply peripheral nerves. Ramon y Cajal, only about 100 years later, discovered the true structure of the peripheral nerves, composed of axons and SCs that are in a symbiotic connection with it [2]. In the following years, with the evolution of electron microscopy, the study of SC morphology has developed continuously, leading to a better understanding of their complex biology.

It is known that nerves in PNS are much easier to regenerate than those in the central nervous system (CNS). Ramon y Cajal sensed very well that there is a "symbiosis" between the axon and the Schwann cells. Kidd et al. [3] described the Schwann cell as one of the largest and most complex cells in the body, which can develop and evolve rapidly after injury. The origin of the Schwann cell is in the

neural crest, and this differentiation is made by the regulation of Sox10 but also in the presence of Notch and endothelin signaling [4, 5].

After a peripheral nerve lesion, a series of cellular changes occur at both axons and Schwann cells, a phenomenon known as Wallerian degeneration: axonal degeneration and myelin destruction, followed by a dedifferentiation (an immature-like phenotype of SCs) and proliferation of Schwann cells [6].

The purpose of this chapter is to highlight the extremely important role of the Schwann cell in the regeneration of the peripheral nerve and its extraordinary plasticity in order to ensure this phenomenon.

2. Peripheral nerve injury

What does peripheral nerve injury mean? This could mean a mechanical trauma, transection or crush, or a pathological condition, when could be affected sensory nerves, motor nerves or autonomic nerves. A peripheral neuropathy may affect one or many nerves, axon, or myelin in the first stage.

In the nerve transection, all nerve fibers are affected, while in a disease manifestation, only a number of nerve fibers are affected, others being normal (**Figures 2A** and **4**).

Very briefly, in peripheral neuropathies, it may be an axonal primary damage or a myelin sheath primary damage. After a period both components of the nerve fiber are affected.

Primary axonal degeneration, whether it is nerve transection or a pathological manifestation, is essentially the same: it starts with a Wallerian degeneration in the distal part of nerve (**Figure 1**), following the myelin destruction. On semithin transverse

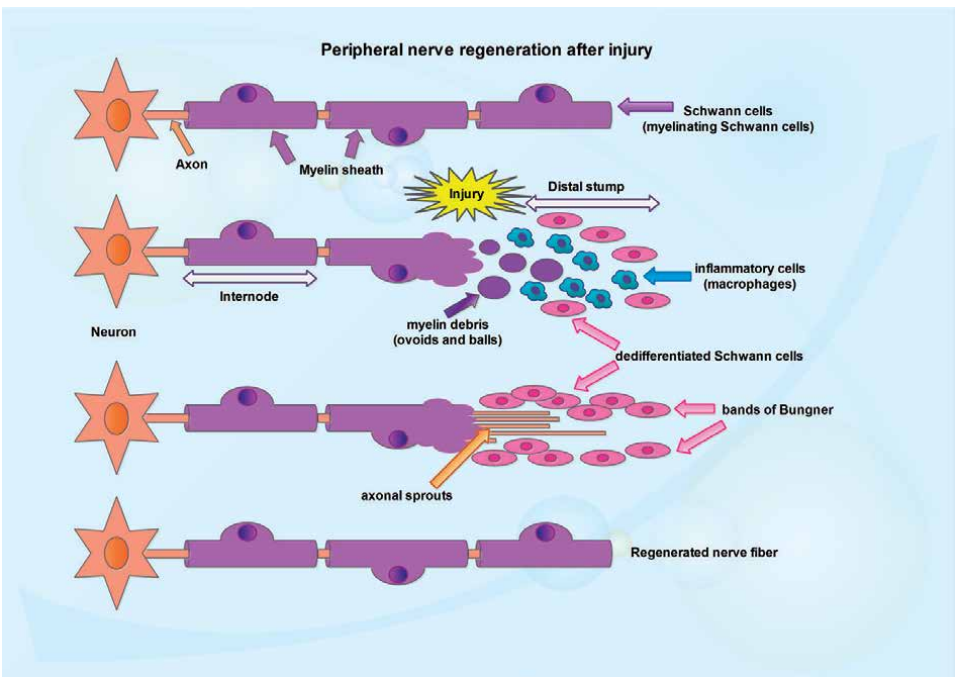

Figure 1.
Wallerian degeneration. After injury, axon and myelin sheath in the distal stump degenerate. Macrophages migrate to the site of lesion and with proliferating Schwann cells remove myelin debris. After the debris has been removed, dedifferentiated Schwann cells align forming bands of Bungner, guiding axonal sprout regeneration.

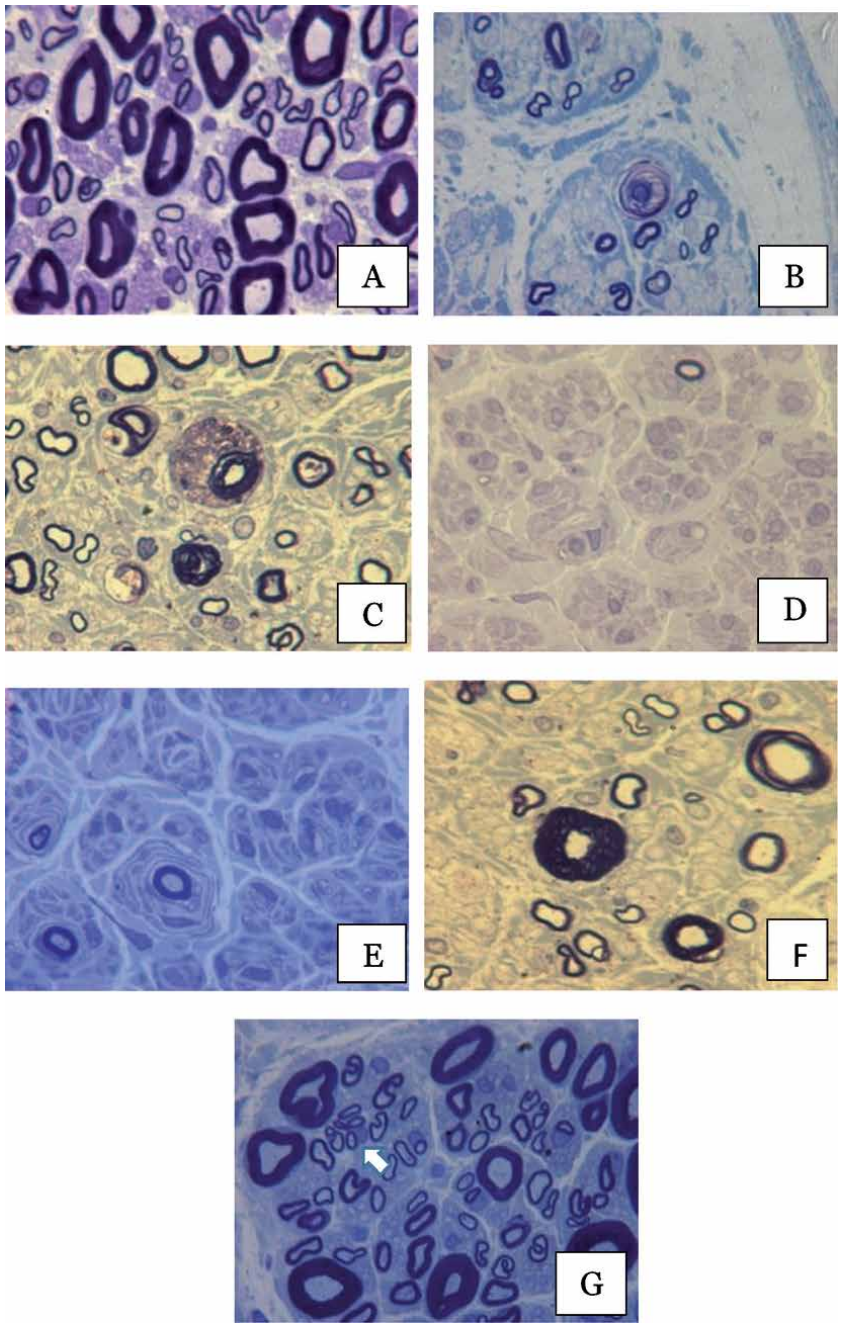

Figure 2.
Peripheral nerve pathological modifications (sural nerve biopsy): (A) a very mild affected nerve, with a normal fiber density; some myelinated fibers with small and medium mean diameter with demyelination; (B) a severe axonal destruction, with disappearance of many large diameter axons and with a low-fiber density; a degenerated axon is present; (C) many degenerated axons and demyelination present in the rest of myelinated fibers; (D) a very severe neuropathy with disappearance of most of the myelinated fibers; (E) some small myelinated axons with onion bulbs; (F) a hypermyelinated fiber in an HNPP case (tomacula) in the center of the image; (G) regeneration aspect: cluster of small axons (arrow). Semithin cross sections stained with toluidine blue; (under oil immersion – 60× Objective).

sections (**Figure 2B** and **C**) and in electron microscopy images (**Figure 3**), the affected nerve fibers are seen to be in a process of necrobiosis. In electron microscopy images, autophagic vacuoles are seen, near the axon (**Figure 3A**) or in the exterior layer of SC,

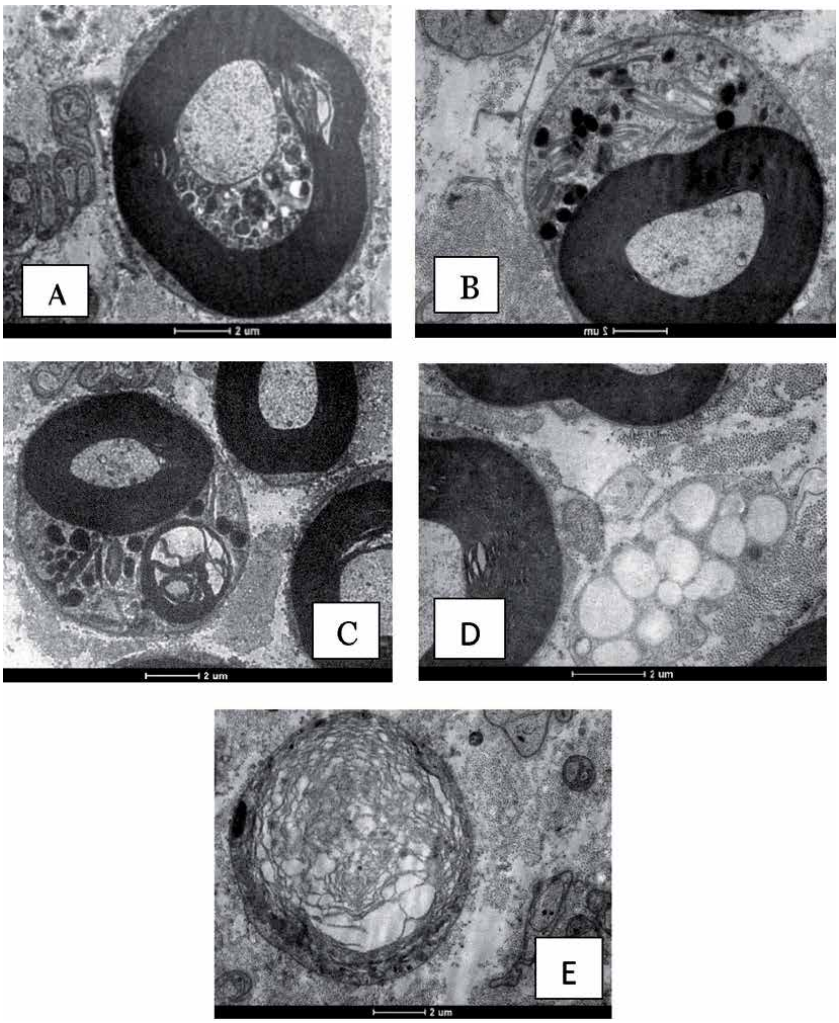

Figure 3.
Electron microscopy aspects of axonal degeneration (sural nerve biopsy). (A) A myelinated axon showing an autophagic vacuole between axon and myelin sheath. (B) A myelinated axon with an autophagic vacuole in the Schwann cell exterior cytoplasma: small myelin debris are seen. (C) The same aspect: an autophagic Schwann cell with many smaller or bigger fragments of myelin inside. (D) A macrophage with lipid droplets is present near myelinated axons. (E) Total myelin degradation; only irregular laminated structure is present, with no axon (cross sections; bar = 2 μm).

under the basal lamina (**Figure 3B** and **C**) and macrophages (**Figure 3D**). After the destruction of the nerve fiber, only irregular structures of myelin residues can be seen (**Figure 3E**) or myelin debris like ovoids and balls (**Figure 4B** and **C**). If it is a chronic process, many nerve fibers disappear, the density of myelinated fibers being very low (**Figure 2D** and **E**). When the myelin is affected in the first step, not all Schwann cells are suffering in the same time. One internode with a very thin sheath between two normal internodes may be observed: segmental demyelination (**Figure 4A** and **B**). When a myelin protein, PMP22, is genetically affected, in hereditary neuropathy with pressure palsies (HNPP), the nerve biopsy shows demyelination and focal hypermyelination structures, tomacula (sausage-like) (**Figures 2F** and **4D**). In hypertrophic neuropathies, like Charcot-Marie-Tooth disease type 1A (CMT 1A) and chronic inflammatory demyelinating polyneuropathy (CIDP), some structures named "onion bulbs" are present, a result of concentric layers of Schwann cell processes and collagen around the axons (**Figure 2E**). It is a repetitive segmental demyelination and myelin regeneration.

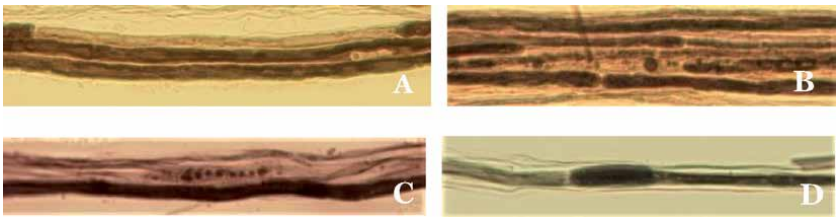

Figure 4.
Teased nerve fiber (sural nerve biopsy) panel. (A) A nerve fiber with segmental demyelination near two other normal myelinated fibers. (B) Near normal fibers, a fiber with segmental demyelination (a thin internode) and a fiber with few myelin ovoids and balls (axonal degeneration). (C) More myelin ovoids in an axonal degeneration. (D) A tomacula in myelin sheath of a nerve fiber.

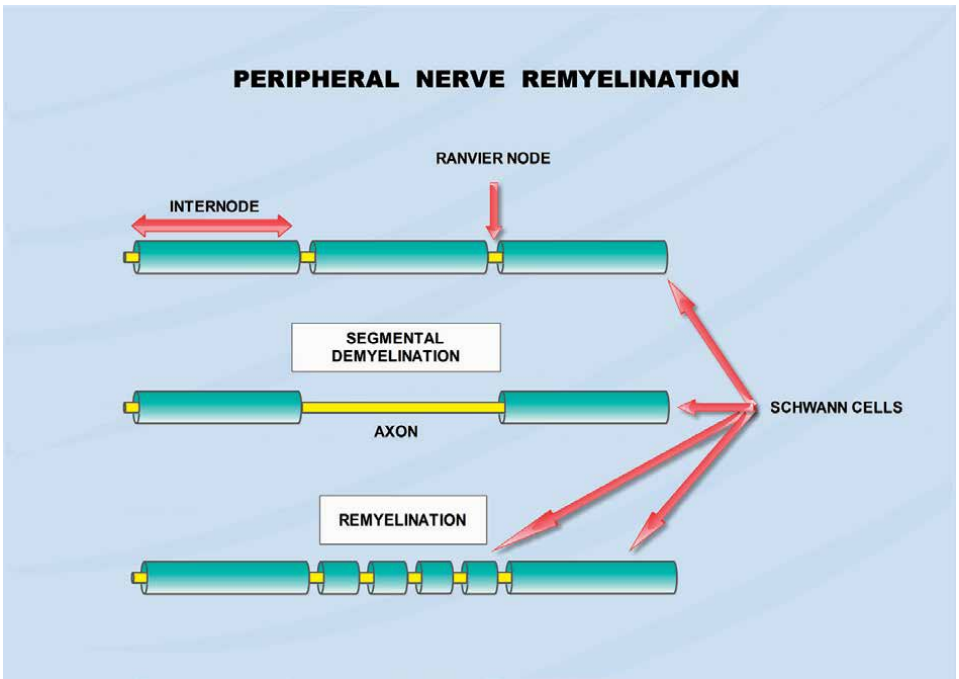

Figure 5.
Peripheral nerve remyelination. In demyelinating peripheral neuropathies, the segmental demyelination is often seen. Following a Schwann cell degeneration, the lost myelin internode is replaced by some Schwann cells which generate myelin sheaths, resulting in many shorter internodes.

After a segmental demyelination, along the affected internode, several Schwann cells arrive which begin to remyelinate this portion, the sign of remyelination being more short internodes (**Figure 5**).

The sign of axonal regeneration is observed on semithin sections and consists of the presence of some clusters of axons with the same small mean diameter and thinner myelin sheath (**Figure 2G**).

After these images sowing just few aspects of pathological degradation of peripheral nerve, focusing on myelin sheath damage, let's take a closer look at what happens in the Schwann cell, at the cellular and molecular level.

3. Myelin protein gene expression in peripheral nerve after injury

Investigating the evolution of the main proteins that enter the composition of myelin sheath during and after nerve injury has been a subject of study for many

scientists. These proteins are P zero (P_0), myelin basic protein (MPZ), and P2. The first two play an important role in maintaining the integrity and compactness of the myelin sheath. P2 is a lipid-binding protein and participates in fatty acid elongation and transport during the myelination process [7]. Myelin associated glycoprotein (MAG) is a transmembrane protein that is found in the periaxonal region and participates in SC-axon contact organization. It seems to be involved in the myelination process after injury [8]. P_0 and MBP mRNA in the distal nerve portion after transection were found to be 20% lower than normal levels but have had normal levels after crushing [9, 10]. In the absence of a contact between SCs and the axon, the levels of mRNAs of P_0 and MBP remained low, and mRNA of MAG was undetectable, long time after nerve transection, whereas MAG mRNA was undetectable after lesion; in the case of a crush injury, after a sudden and short decrease, the mRNA levels of these proteins were found to increase rapidly afterwards [10, 11].

4. Biological aspects of Schwann cell

To understand what plasticity of Schwann cells means, we need to understand what the starting point is for their differentiation and evolution.

4.1 Schwann cell differentiation and development

During development, SCs surround bundles of axons and support them to outgrow by releasing growth factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT3) [12–14]. It follows a "radial sorting" of axons by extension of cellular process from Schwann cells, which begins to divide axon bundles into smaller ones and finally separate the neighboring axons with cell cytoplasm. Thus two types of fibers are formed: (i) unmyelinated Remak fibers, in which SC surrounds several small-sized axons (sensory and autonomic) and does not produce myelin, and (ii) myelinated fibers in which each large-sized axon is surrounded by a SC cell, 1:1 relationship, and a myelin sheath is formed by SC membrane spirally wrapping the axon [15]. Mesaxon is termed the point where the plasma membrane apposition is formed where the first encircling process meets itself. Remak SCs maintain the proliferative capacity of all the life [16].

During this stage, changes in cell morphology and gene expression occur, mediated by the transcription factor Krox-20 (or Egr-2) [17–19].

4.2 Interactions between Schwann cells and axons

The differentiation of Schwann cells is controlled by some **growth factors** among which the most important are in the neuregulin family. Neuregulins (Nrgs) are transmembrane proteins that signal through ErbB tyrosine kinase receptors [20]. Axonal neuregulin-1 (Nrg1), produced in many isoforms by alternative splicing (heregulin, glial growth factor, sensory and motor neuron-derived factor), interacts with ErbB2/ErbB3 receptors tyrosine kinase expressed on Schwann cells [21–25]. ErbB2 and ErbB3 combine to act as heterodimers and efficiently bind Nrg1. **Nrg1/ErbB** signaling axis has a critical role in Schwann cell development (for review [26–28]) like survival, proliferation, migration, differentiation, and myelination [26, 29–32].

Nrgs need protease involvement for Nrg1-ErbB interactions because Nrgs are synthesized as single-pass transmembrane proteins and shed from the cell surface

by the proteolytic cleavage, thus permitting the interaction with ErbB receptors across the periaxonal space [33, 34].

Another enzyme implicated in Nrg1 cleavage is beta-amyloid converting enzyme (BACE1), a **beta-secretase** present in axon [35, 36]. An *in vivo* study showed that the BACE1-null mice presented reduced rates of Nrg1 cleavage and decreased PNS myelin, a low capacity of myelination with axons with a thinner myelin sheath [35].

An effect opposite to the BACE activity has tumor necrosis factor-alpha-converting enzyme (TACE), a neuronal alpha-secretase, cleaving Nrg1 into an inactive form [37]. TACE genetic inactivation in motor neurons caused hypermyelination like in Nrg1 overexpression.

Another factor that is essential in SCs-axon interaction, with a protection role for the axon, is **Schwann cell basal lamina**. The basal lamina together with extracellular collagen fibrils protects axons from extension and compression injuries. They provide good support for axonal outgrowth and guidance (reviewed by [38]). Basal lamina defines also Schwann cell orientation in axonal myelination [39]. More of this, SCs require axonal contact for secreting the components of basal lamina, so the relationship of axon-SCs via basal lamina is interactive and reciprocal [40, 41].

All these interactions described above are very important and may be modulated in the control of nerve regeneration.

5. Schwann cell plasticity

PNS has a very good regenerative capacity, and this is largely due to Schwann cells that develop a high plasticity and can contribute very quickly to the regeneration of peripheral nerves after injury whether it is a trauma or a pathological condition. In these cases, SCs have the ability to transform into an immature-like form, which drives subsequent regeneration of the nerve. These processes of dedifferentiation into non-myelinating cells and redifferentiation after injury are characteristic of these glial cells in PNS, and in the last decade a significant progress has been made in the study of the molecular mechanisms and signaling pathways that regulate this plasticity (reviewed in [42]). More of this, the myelinating and non-myelinating SCs remain bipotential cells all the time, as demonstrated by grafting or nerve cross anastomosis experiments [43–45]. Many experimental studies on transgenic animals have shown that after nerve cut or crush, both types of SCs reprogram into proliferative progenitor-like repair SCs [46, 47]. This phenomenon involves downregulation of pro-myelinating genes, such as early growth response 2 (Egr-2 or Krox-20), POU domain class 3 transcription factor 1 (Pou3f1 or Oct-6), and myelin protein zero (MPZ)/myelin basic protein (MBP). There is also an upregulation of markers of dedifferentiated (immature) SCs like low affinity neurotrophin receptor (p75NTR), c-Jun, or glial fibrillary acidic protein (GFAP) [6].

After Wallerian degeneration following nerve injury, a downregulation of pro-myelinating genes occurs, and the myelin clearing phenomenon begins after myelin sheath disorganization, through a mechanism of autophagy or myelinophagy [48]. Macrophages also participate in this process, phagocytosing myelin and axonal debris. The recruitment of macrophages is also done by SCs [49–51].

One of the major problems of human SCs is that as their regenerative capacity decreases in time, they can no longer sustain axonal growth, and their numbers decrease greatly (reviewed in [52]).

Regarding the plasticity of Schwann cells, although not covered by this chapter, we just want to mention here that SC precursors can generate many and different

cell types during embryogenesis, besides myelinating and non-myelinating SCs, such as endoneurial fibroblasts, melanocytes, and neurons [52].

5.1 Schwann cell dedifferentiation

After injury, SCs reacquire some capabilities from early development, like proliferation, production of growth factors, sorting, and myelination. A good review regarding the biology of Schwann cells is the one made by Kidd et al. [3].

SC behavior and fate is regulated by two sort of interactions: SCs-axon and SCs-extracellular matrix/basal matrix. After 48 hours following axonal transection, SCs downregulate the production of myelin protein mRNAs [53] and upregulate trophic factors and cytokines [12–14] like NGF, BDNF, GDNF, and LIF, molecules necessary in axonal regeneration promoting into distal stump (reviewed in [54]). After axonal injury/transection, the axon is rapidly destroyed by a nonapoptotic autonomous mechanism [55]. SCs begin myelin degradation after axon injury, disassembling first the myelin internode starting with Schmidt-Lantermann incisure swelling [56, 57], following the dissolution of myelin in bubbles, ovoids, and balls. Macrophages finish the myelin degradation by phagocytosis [58]. It is not known exactly how much the SCs contribute to myelin degradation compared to macrophage participation, but it seems that it depends on the volume of the internode [59, 60]. During myelin degeneration, changes occur in the SC microtubule network, lysosome, and endosome positioning [61].

After nerve crush or transection, between the two stumps, over the lesion site, fibroblasts form a bridge, interacting with SCs [62]. The newly formed vasculature participates also in guiding the growing axons through this bridge to the distal end [63]. After a period of persistence of distal nerve stumps, distal axons disappear and dedifferentiated SCs proliferate, align, and begin emitting processes, forming the bands of Bungner (**Figure 1**), offering a physical and trophic support for the regrowth of axon [44, 60].

After the axonal regeneration, SCs differentiate once more in non-myelinating and myelinating cells to finish the functional recovery of the nerve. The regenerated myelin internodes (**Figure 5**) are shorter and thinner than the rest of the original ones in the proximal part of nerve [64].

5.2 Molecular mechanisms which control SC plasticity

The molecular mechanisms that regulate SC plasticity are very complex and widely described in many studies in recent years (reviewed in [42]). Here we will briefly mention them.

5.2.1 Transcriptional factors

One important transcriptional factor in SC reprogramming is **c-Jun**. Although it is downregulated or absent in the differentiation of SC, under pathological conditions c-Jun is particularly upregulated as described in various peripheral neuropathies [65–69], being a cross-antagonist of Krox-20 (a pro-myelinating transcription factor). c-Jun take part at the myelinophagy process [47] and participate also in the macrophage recruitment following nerve injury [70].

Another transcriptional regulator is **NICD**, an intracellular domain generated from neurogenic locus notch homolog protein (**Notch**) cleavage. SC proliferation and generation of immature SCs are controlled by Notch. But the same Notch is a negative regulator of myelination [71].

Nuclear factor kB (**NF-kB**), a transcription factor which regulates many physiological processes especially the inflammatory response, is very important for SC differentiation and myelination as *in vitro* studies showed [72–74].

In the recent years, a transcriptional repressor, **Zeb2**, has been investigated, and the researchers showed that it is implied in SC differentiation and myelination. The lack of Zeb2 in SCs results in a failure of SC maturation and in absence of myelin membranes [75].

Other factors which are overexpressed in SC dedifferentiation are **Sox-2**, paired box protein 3 (**Pax-3**), early growth response proteins 1 and 3 (**Egr-1** and **Egr-3**), and DNA-binding protein inhibitor 2 (**Id2**) [66, 76, 77]. Sox-2 is also necessary for the nerve bridge formation after nerve injury [62].

mTOR complex 1 (**mTORC1**) (reviewed in [78]) has a significant role on the transcriptome by controlling transcription factors [79–82]. It promotes anabolism, counting mRNA translation, and purine and pyrimidine synthesis [83, 84]. mTORC1 is necessary in radial sorting of axons by SCs, biosynthesis of lipids, and, on this basis, myelin growth [85, 86]. The mTORC1 activity is higher before myelination onset and decreases when myelination starts [87–89].

5.2.2 Mitogen-activated protein kinase (MAPK) family proteins

In the distal stump of the peripheral nerve after injury SCs respond by activating MAPK proteins like extracellular signal-regulated kinase (Erk), c-Jun N-terminal kinase (JNK), and p38 MAP kinase [66, 90–95].

Ras/Raf/Erk signaling in SC dedifferentiation was studied for the first time by Harrisingh et al., and they showed that the Raf activation suppresses the differentiation of primary SCs induced by cyclic adenosine monophosphate (cAMP) [91]. Raf is an activator of Erk. The authors demonstrated that the activation of Ras/Raf/Erk pathway induced demyelination in an *in vitro* study on cocultured cells—SCs and neurons from dorsal root ganglia.

Erk activation is a pro-myelinating factor, and if Erk is inhibited, the SC differentiation and myelination are blocked, showed many *in vivo* studies [96–98].

In conclusion, Erk signaling is required in differentiation (Erk low levels) but also in dedifferentiation (high Erk levels) of SCs after nerve lesion [99, 100].

JNK, another MAPK protein, is implied in SC functions, so when c-Jun is activated by JNK, the migration and proliferation of SCs are produced [19, 101, 102].

Without insisting, we would like just to remember other MAPK proteins and signaling pathways involved in SC plasticity: **p38MAPK**, **PI3K/Akt/mTOR** signaling (reviewed by [42]).

5.2.3 TLRs signaling

After nerve injury, inflammation is an important phenomenon that must be considered. Thus, Toll-like receptors (TLRs) are key factors in initiating the immune response. A number of such receptors are expressed by SCs: TLR3, TLR4, and TLR7 [103]. Some experimental studies showed an upregulation of TLRs following nerve injury, the effect being the inflammation trigger with macrophage recruitment and activation and myelin clearance via SCs [50, 104, 105].

5.2.4 Nrg1/ErbB2/3 signaling

SCs express receptors for axonal neuregulins, as it is showed in Ssection 2.2. The neuregulin/Erb2/3 signaling is strongly involved in immature SC

development but not in the regulation of adult SC proliferation after injury. An *in vivo* study on erbB2 wt/lacZ (with highly reduced ErbB2 levels in adult sciatic nerves) mice showed that after sciatic nerve transection, SC proliferation is not affected in adult ErbB2-conditional null nerves. More of this, the maintenance of myelinated peripheral nerves did not require ErbB2 function [106]. Other studies demonstrated that ErbB2 activation after sciatic nerve axotomy induced SC demyelination [107].

Neuregulin Nrg1 is still necessary for adult SC evolution after nerve injury [108, 109]. The absence of Nrg1 in adult axons results in remyelination defects after nerve crush experiments and also in a slower axon regeneration [110].

6. Therapeutical approaches based on Schwann cell plasticity

Although the peripheral nerve has a much greater regenerative capacity than the CNS nerve, the clinical recovery of patients with peripheral neuropathies is difficult, slow and often incomplete. Moreover, this capacity decreases with age.

The rate of nerve regeneration is approximately 1 mm/day, depending on the site of the lesion and on the patient age. SC plasticity diminishes with age, showing an altered expression of c-Jun [111] and a weak regenerative capacity [112, 113].

Understanding the signaling pathways that govern SC reprogramming and plasticity is essential for nerve repair and therapy.

For example, modulating Nrg1/ErbB signaling may improve myelin clearance, axonal regeneration, and finally functional nerve recovery after injury. An inappropriate overactivation of this pathway may lead to demyelinating neuropathies or tumors like neuroepithelioma and neuroplastic SC line [114, 115]. Experiments on transgenic mice with overexpression of Nrg1 showed hypertrophic neuropathies and malignant peripheral nerve sheath tumors [116]. The excessive activation of ErbB2 by *Mycobacterium leprae* determines one of the symptoms of leprosy, an important peripheral nerve demyelination [117]. In Charcot-Marie-Tooth 1A, abnormal demyelination and axon loss were prevented by Nrg1 therapy during early postnatal period in a rat model [118].

Another approach to stimulate SC regeneration and peripheral nerve functional recovery is the exogenous modulation by electric stimulation with low frequencies, photomodulation with low-level laser, and pharmacotherapy (with pharmacological agents, growth factors, bioproducts, or hormones) (reviewed by [119]).

7. Conclusions

Understanding Schwann cell biology and its extraordinary plasticity can lead to the development of new therapeutic approaches in peripheral nerve pathology and in the improvement of treatment methods in the case of traumatic nerve lesions. Peripheral neuropathies cause a significant morbidity and a decreased life quality. A better understanding of the many SC signaling pathways represents a very important approach for nerve regeneration as long as we have seen that SC is the main engine in nerve damage and repair after injury.

The recovery of the peripheral nerve, although better than that of the CNS nerve, is still quite complicated, difficult many times, and it is never perfect until the end. But in the last years, a huge amount of scientific data drew attention to the role of growth factors, transcriptional factors, inflammatory factors, hormones, and even exogenous modulation factors in the regulation of Schwann cell and of Schwann cell-axon interrelations, a complex integrated system.

It is expected that studies regarding SCs plasticity in peripheral nerve regeneration will continue and expand, improving not only the scientific knowledge but also a targeted more effective therapies, based on the pathology, personalized treatment and specific response of patients.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 4

Non-Myelinating Schwann Cells in Health and Disease

Octavian Ioghen, Emilia Manole, Mihaela Gherghiceanu, Bogdan O. Popescu and Laura Cristina Ceafalan

Abstract

Non-myelinating Schwann cells (NMSCs) are one of the two major phenotypes of Schwann cells. NMSCs are of different types and have various locations. In the peripheral nervous system, NMSC, named Remak Schwann cells (RSC), accommodate multiple small-caliber axons, forming Remak bundles. NMSC, named perisynaptic/terminal Schwann cells, are found at the distal end of motor nerve terminals at the neuromuscular junction (NMJ). Thus, NMSCs proved to serve different functions according to their distribution such as maintenance of the axon and NMJ, peripheral nerve regeneration, or remodeling of the NMJ. Schwann cells (SCs) retain their proliferation capacity in the case of nerve injury or demyelination and provide support for the neuronal cells through paracrine signaling. Here we present an overview of their phenotypes and tissue distribution focusing on their emerging involvement in various peripheral nerve diseases.

Keywords: non-myelinating Schwann cells, Remak cells, perisynaptic Schwann cells, demyelination, nerve regeneration

1. Introduction

Among the Schwann cells (SCs), non-myelinating Schwann cells (NMSCs) represent an important category that was not extensively studied, although the gathered data demonstrate they are essential for axon maintenance and neuronal survival in the peripheral nervous system (PNS). Extending the knowledge on NMSCs biology could open new perspectives on the normal functioning of PNS as well as for better understanding the mechanisms underlying various pathological conditions and further on for developing new therapeutic approaches in peripheral nerve diseases.

The NMSCs encompass two major cell types, according to their distribution: Schwann cells of Remak fibers and the specialized perisynaptic/terminal Schwann cells at neuromuscular junctions (NMJ). In addition in this category are also included the glial cells found in some sensory transducers, such as the Pacinian and Meissner's corpuscles, as well as in the sensory and autonomic ganglia, where they are called satellite cells [1]. In pathological circumstances like axonal loss or demyelination, the former myelinating Schwann cells also become a class of NMSCs. Conversely, all NMSCs retain the potential to myelinate [2], if they receive the appropriate cues, most of which derive from the associated axons, along with some fate-controlling genes that act cell-autonomously within SCs [3, 4].

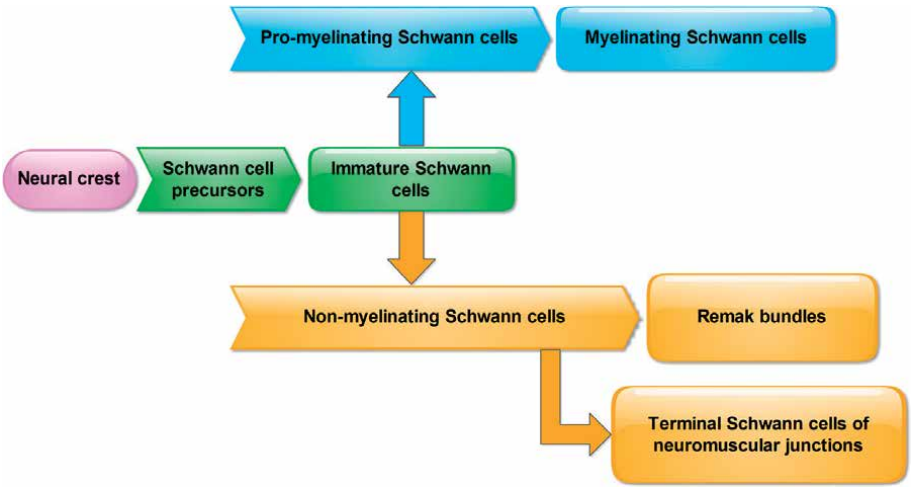

Figure 1.
Schwann cell lineage. SCs derive from the neural crest cells, after contacting nascent nerves during embryogenesis. Neural crest cells give rise to SC precursors, in early embryonic nerves which further differentiate into immature Schwann cells, in late embryonic and perinatal nerves. Postnatally, iSch will further differentiate either toward myelinating cells or non-myelinating cells according to axon-derived signals. The myelinating cells form the myelin sheath of large axons. The non-myelinating cells ensheath small axons forming unmyelinated fibers, called Remak bundles, or they migrate toward the neuromuscular junctions, covering the axon terminals, where they become terminal/perisynaptic/teloglia Schwann cells.

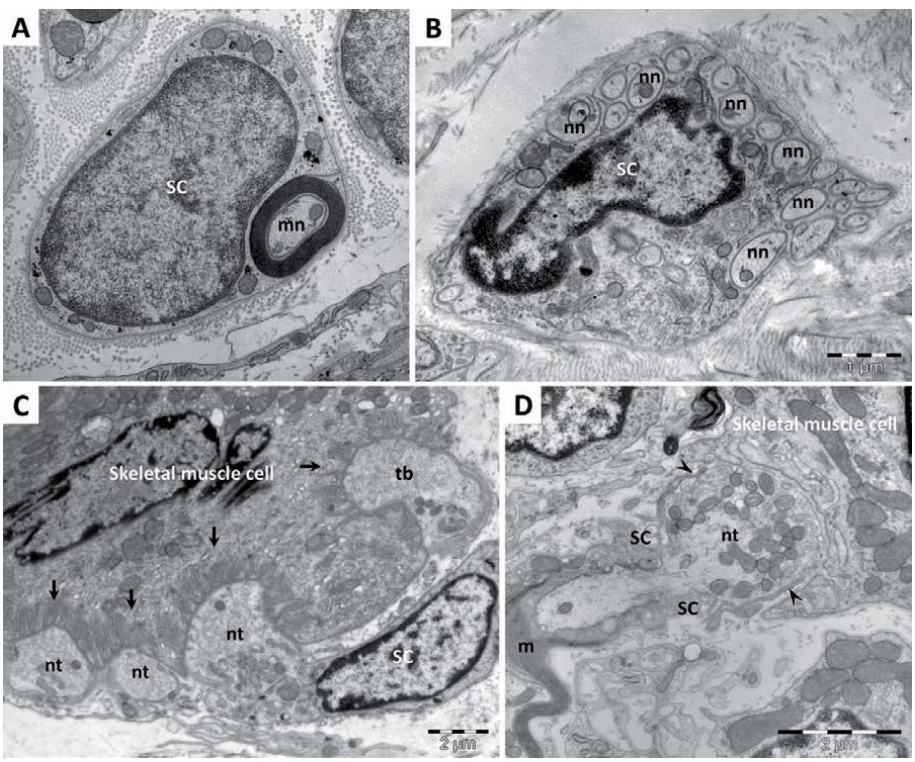

Figure 2.
Transmission electron microscopy of myelinated (mn, in A) and nonmyelinated (nn, in B) axons of peripheral nerves embedded in the cytoplasm of Schwann cell (Sch). C and D show the Schwann cells and nerve terminals (nt) in neuromuscular junction. (C) The motor end plate formed by folded sarcolemma (junctional folds, arrows) accommodates knob-like terminal buttons of the motor nerve (nt). (D) The myelin sheath (m) covering the axon ends (nt) in the vicinity of neuromuscular junction and Schwann cell extends into the synaptic cleft (arrowheads).

All Schwann cells derive from multipotent progenitor cells of the neural crest (**Figure 2**). The fate decision mechanism of SCs to become myelinating cells or to form RSCs is not fully understood, although the plasticity of SCs in various studies is recognized. Thus, some studies proved that if myelinated nerve segments are grafted, on a nerve that contains especially unmyelinated fibers, transplanted SCs do not myelinate, and equally, RSCs can produce a myelin sheath when they are grafted onto a myelinated nerve [2, 5].

After contacting nascent nerves during embryogenesis, neural crest cells give rise to SC precursors (SCP), which further differentiate into immature Schwann cells (iSC), in late embryonic and perinatal nerves (**Figure 1**). After birth, iSC will further differentiate either toward myelinating cells or non-myelinating cells according to axon-derived signals. The myelinating SCs form the myelin sheath of large axons (**Figure 2A**). The non-myelinating cells ensheath small axons forming unmyelinated fibers, called Remak bundles (**Figure 2B**), or they migrate toward the neuromuscular junctions, covering the axon terminals, where they become terminal/perisynaptic/teloglia SCs (**Figure 2C** and **D**).

This chapter addresses the main types of NMSCs, in terms of biological aspects and their role, aiming to highlight their importance for a better understanding of pathological mechanisms underlying various peripheral nervous system diseases.

2. Types of NMSC

2.1 Remak Schwann cells

Robert Remak first described the unmyelinated nerve fibers using the nerve fiber teasing technique in 1838 [6], so, in his honor, they were named "Remak fibers."

In the PNS most nerve fibers are unmyelinated [1], formed by RSCs accommodating a variable number of small-caliber axons (less than 1 μm diameter) (**Figure 2B**).

RSCs do not produce myelin, but they are essential for normal PNS development and functioning.

During PNS formation, pockets with multiple axons within a single mesaxon can be encountered. This aspect occurs only occasionally in normal adult Remak fibers where the small diameter axons of C nerve fibers (sensory/afferent), postganglionic sympathetic fibers, and some preganglionic sympathetic or parasympathetic fibers are accommodated in separate grooves of longitudinally interconnected RSCs forming the Remak bundles. Each RSC surrounds many axons, during radial sorting, forming a mesaxon for each axon. It is uncommon for an axon to be in direct contact with the basement membrane of the Schwann cell [4].

The number of axons surrounded by a RSC varies depending on the type of nerve fibers or a particular region along them. Thus, there is a higher number of axons exiting the dorsal root ganglion than in the distal segments of the peripheral nerve. In the cutaneous nerves, the number of axons per RSC decreases as they approach the skin [7], suggesting the existence of specific mechanisms regulating RSC-axons association as they approach their target. Moreover, the distribution of the axons within the Remak bundles varies along the peripheral nerve, with multiple axons within one pocket of the RSC toward the dorsal root and completely isolated axons in the distal segments [8].

There are studies reporting the presence of few short, myelinated internodes along a unmyelinated fiber especially in older animals [9].

Thus, it appears that the "ensheathment fate" of axons to either become myelinated or unmyelinated fibers relies on local/environmental cues. One of the most

extensively studied is the neuregulin 1 type III signaling through ErbB receptors, an axolemmal myelin-inducing factor [3] that promotes the formation of a mesaxon for each unmyelinated axon as well as SC differentiation into myelinating cells, depending on the expression level [10].

Another feature of unmyelinated nerve fibers is that axons may switch between neighboring Remak bundles along the nerve.

Moreover, a RSC can surround axons with different functions, for example, both sensitive and sympathetic axons, both axons expressing TrkA (tropomyosin receptor kinase A) receptors with a high affinity for nerve growth factor (NGF) and axons expressing RET (rearranged during transfection) receptors that respond to glial cell line-derived neurotrophic factor (GDNF) and artemin or axons derived from different dorsal ganglia [1].

2.1.1 Remak Schwann cell differentiation

The RSCs differentiation is governed, at least in part, by neuronal cues, especially by the signaling pathway neuregulin 1 type III (Nrg1-III)/ErbB2/ErbB3 receptor cascades. However, a number of cell-autonomous genes also contribute to SCs differentiation toward RSCs, one of which is gamma-aminobutyric acid type B1 receptor (GABBR1) [4].

SCs derive from the neural crest cells, after contacting nascent nerves during embryogenesis. Neural crest cells give rise to SCP, in early embryonic nerves, which further differentiate into iSCs, in late embryonic and perinatal nerves. Postnatally, iSCs will further differentiate either toward myelinating cells or non-myelinating cells according to axon-derived signals. The myelinating cells form the myelin sheath of large axons (larger than 1 μm diameter). The non-myelinating cells ensheath small axons forming unmyelinated fibers, called Remak bundles, or they migrate toward the neuromuscular junctions, where they become terminal/perisynaptic/teloglia Schwann cells (**Figure 3**).

2.1.1.1 Neuregulin

There are four distinct genes for neuregulins, but neuregulin 1 NRG1 is the best studied. NRG1, also known as glial growth factor (GGF), is a growth factor with EGF domain homology known to induce growth, differentiation, and migration of Schwann cells throughout development [10, 11]. NRG1 has three isoforms out of which type III is considered to be the most important signaling molecule for SC-axon interactions. NRG1 type III is produced by neurons and is released from axons by proteases, such as BACE1, or may remain anchored to the axonal membrane. NR1-III interacts with high-affinity tyrosine kinase receptors ErbB2/ErbB3 heterodimers, triggering the activation of downstream pathways, such as Ras/MAPK and PI3K/Akt SCs. Stimulation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) cascade was proven to lead to the suppression of myelinating state [12] through ErbB2 and ErbB3 receptors that are expressed in Schwann cells [13]. The NRG1-ErbB signaling pathway seems to play a crucial role in the SCs lineage for both myelinating and non-myelinating SCs and promotes SCP precursor survival after birth as well as during in vitro culturing [10, 14].

However, recent studies showed that in transgenic animal models where NRG1 is conditionally ablated during postnatal life, there is no reduction in the number of sensory axons but larger, unordered Remak bundles with polyaxonal pockets, where axons are not separated by SC processes, are formed, and some large-diameter

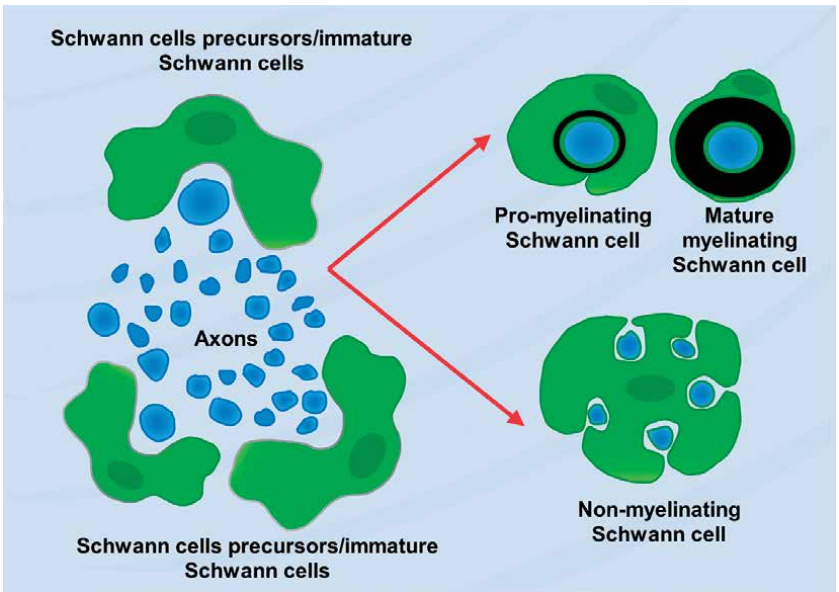

Figure 3.
Schwann cell development and maturation: their role in the evolution of myelinated and unmyelinated peripheral nerve fibers. Schwann cell precursors differentiate into immature Schwann cells which start the process of "radial sorting". A pro-myelinating Schwann cell envelops a large axon and becomes a myelinating Schwann cell. An immature Schwann cell which ensheaths many small axons becomes mature non-myelinating Schwann cell, forming a Remak bundle.

axons lose the myelin sheath. Only the sensory function was affected, without changing the survival and axonal maintenance of the neurons [15]. However, after nerve injury, RSCs re-establish normal Remak bundles, suggesting that during adulthood, after the basal lamina was established, axonal sorting is no more required [16].

Another experimental in vivo study on mouse sciatic nerve showed that NRG1 type III Erb2/Erb3 signaling regulates the morphological changes of the SCs. The study used a NRG1 type III knockout mouse model (+/−) with a low expression of NRG1 type III, which produced Remak bundles with a higher number of axons and smaller spaces between axons [17].

2.1.1.2 Genes acting cell-autonomously in Schwann cells

A number of studies have shown that there are certain genes that control SCs fate [4, 12, 18, 19] and that they act cell-autonomously in SCs. There are genes that can trigger upregulation of NRG1 during differentiation after injury, thus stimulating remyelination and redifferentiation of SCs [20].

An important genetically determining factor during SCs development is the gene for gamma-aminobutyric acid type B1 receptor (GABBR1), which is active mainly in RSCs as compared to myelinating SCs [21]. An in vivo experimental research showed that the absence of *GABBR1* in embryonic SCs leads to an increased number of small-caliber axons and Remak bundles and a decreased number of the large-caliber axons [19]. Furthermore, NRG1-III expression was decreased in GABBR1 mutant animals, in correlation with lower mean diameter axons along with a compensatory gene overexpression and protein levels of ErbB2 and ErbB3. Further studies are needed to analyze the requirement and the mechanism of these cell-autonomous genes in SC fate decision.

2.1.2 Remak Schwann cell maturation

During maturation, RSCs extend cell processes that individually encircle each axon with the plasmatic membrane and cytoplasm, separating it from surrounding axons. Naked axons, which were not completely surrounded by RSC cytoplasm and which come into direct contact with other axons, demonstrate failed RSC maturation after nerve injury [22]. Recent studies have shown that the expression level of a protein that is highly expressed in non-myelinating SCs, neuropathy target esterase (Nte), is correlated with SC developmental maturation and remyelination after neuronal injury. However, this protein is not involved in myelination [23].

Other proteins, such as mTOR [24–26], or G-G protein-coupled receptor Gpr126/Adgrg6, through laminin-211 and collagen type IV interactions, are required for both myelinating and non-myelinating SCs growth and function, during developmental stages as well as after nerve injury. Gpr126 controls radial sorting, myelination, SC-axon interactions, as well as Remak bundle formation [27–30].

In SCs, both deletion and overexpression of mTOR complex I adapter (Raptor) disrupts Remak bundle formation by increasing the number of axons in Remak bundles, with many naked axons [26], or decreasing the number of axons in Remak bundles and aberrant wrapping of multiple membrane-layered axons by RSCs, respectively [24, 31].

2.1.3 Role of Remak Schwann cells

The absence of myelin gives Remak fibers a certain plasticity, sprouting, and growth abilities that exceed that of myelinated fibers. That is why they are found especially in PNS, where the risk of physical injuries is much higher than in the CNS.

Although Remak fibers are found mainly in the PNS, they are also found in the CNS, associated with unmyelinated fibers in the parallel fiber system of the cerebellum and nigrostriatal pathway [1, 32].

2.1.3.1 RSCs as immune competent cells

NMSCs, like other SCs, can also function as immunocompetent cells playing an essential contribution in mounting and modulating of immune response in certain conditions, by antigen presentation and cytokine secretion, as well as by their direct interaction with immune cells. Moreover, NMSCs express specific pattern recognition receptors (PRR) for the detection of pathogens, such as Toll-like receptors (TLRs) and the nucleotide-binding and oligomerization domain (NOD)-like receptor (NLR) family [33–35].

The crosstalk between immune- and peripheral nerve SCs through a large array of molecules either expressed or recognized by SCs build up the base for nervous-immune system interactions. The subject was extensively reviewed by Tzekova et al. [34]. Moreover, Hu et al. showed that NMSCs located in the thymus develop correlations with thymocytes, lymphocytes, and dendritic cells under normal and pathological conditions. They concluded that NMSCs are highly suitable for studying the local interactions of the PNS and primary lymphoid tissues or organs [36]. The same observations were made by Ma et al. studying the mouse spleen and the interactions between NMSCs and leukocytes [37].

Another role for NMSCs was concluded by the study of Yamazaki et al. which showed that NMSCs maintain hematopoietic stem cell hibernation in the bone marrow niche. They demonstrated that NMSCs proved responsible for activation of TGF-beta latent form. These glial cells, ensheathing autonomic nerves, get in

contact with hematopoietic stem cells and maintain them in hibernation by regulating activation of latent TGF-beta [38].

2.1.3.2 RSCs in nerve injury and regeneration

Transection of a nerve fiber initiates Wallerian degeneration of the distal stump. As opposed to oligodendrocytes, SCs maintain the ability to dedifferentiate to an immature phenotype in response to nerve injury or disease, and they can actively promote the repair and functional recovery. The repair SCs express inflammatory mediators, such as interleukins and TNFα, as well as anti-inflammatory cytokines (IL-10, Epo, or TGFβ) and growth factors shown to promote Wallerian degeneration, macrophage attraction, and axonal regeneration upon nerve injury [34].

A number of molecules have been shown to play important roles in modulating SC behavior after nerve injury.

LDL receptor-related protein 1 (LRP1) is a significant factor involved in the development and maintenance of Schwann Cells, both myelinating and NMSCs [39]. LRP1 is one of the molecules upregulated after various types of peripheral nerve injury.

The study of Campana et al. proved that LPR1 upregulation was directly correlated with local production of TNFα and TNFα/LPR1 signaling is one of the survival mechanisms for SC migration and survival observed in in vitro studies [40].

Another signaling receptor that plays an important role in regulation of Schwann cell-axon interactions is fibroblast growth factor receptor (FGFR). Fibroblast growth factor 2 (FGF2) is one of the essential regulators of peripheral nerve regeneration after injury [41]. Three of its receptors, expressed by Schwann cells and dorsal root ganglia neurons, are FGFR1, FGFR2, and FGFR3 which are all upregulated after nerve injury [42].

One day after nerve transection, all SCs start to proliferate within the basal lamina. One week post-injury, RSCs double in length, and after 4 weeks they are three-fold longer and were called repair-supportive Schwann cells. About 50% of repair cells derive from RSCs. The loss of axonal contact determines cells to branch. They form branches lying parallel to the main cell axis, building cellular columns and Bungner bands distal to injury site and offering the support of regenerating sprouts. They will further differentiate to myelinating cells after regeneration [43].

2.1.3.3 RSCs and sensory nerve fiber pathology

Most unmyelinated C-fibers ensheathed by Remak cells are nociceptors [39]. They transmit pain information to the brain. Thus, the dysfunction of RSC induces an altered transmission of the nociceptive stimuli, which leads to severe neuropathic pain.

The specific loss of GABBR1 in SCs results in an increased number of C-unmyelinated fibers, leading to a hypersensitivity to thermal and mechanical stimuli. There is also an alteration of the locomotor coordination, without any injury. It is not known whether these consequences are caused only by the modification of the unmyelinated axon number [19].

Other in vivo studies showed that after injury, in LRP1 knockout animals, the resulting hypomyelination and impaired RSCs ensheathment lead to motor dysfunction and mechanical allodynia [39] without any traumatic injury. These pathological changes can cause notable painful symptoms such as mechanical allodynia [39]. In a model with partial nerve injury, the LRP-negative mice have a higher degree of RSC apoptosis, an accelerated degeneration, and further more severe pain in the LRP than the nonmutant mice [39]. These findings suggest the involvement

of RSC in the pathophysiology of neuropathic pain and the importance of LRP1 in the physiology of RSC and open the possibility of using RSC as a new therapeutic target in the treatment of neuropathic pain.

In an experimental study in vivo on FGFR1 and FGFR2 single and FGFR1/FGFR2 double conditional knockout mice, Furusho et al. showed that lack of FGFR1 and FGFR2 signaling in NMSCs resulted in sensory axonal neuropathy in unmyelinated C-fibers and the impairment of thermal pain sensitivity [42]. Another study by Chen et al. performed on transgenic mice that postnatally express a dominant-negative ErbB receptor in NMSCs but not in the myelinating ones led to a progressive peripheral neuropathy with loss of unmyelinated axons and heat/cold pain [44]. Altogether, such data suggest the important role of RSCs in in the modulation of pain sensitivity in peripheral sensory neuropathies.

Charcot-Marie-Tooth type 1A (CMTA1A) is a genetic disease of the peripheral nervous system in which demyelination and further aberrant remyelination occur in a repeated cycle, with an "onion bulb" appearance in microscopy. From the clinical point of view, CMT1A is characterized by weakness and muscle atrophy in the lower limbs and later on by sensory loss. Myelinating Schwann cells are classically known to be impaired in CMT1A, but it seems that there is also an impairment of the RSC [45]. A proliferation of RSC takes place as a response to the degeneration of the myelinated axons that appear to secrete mitogenic factors [45]. Unexpectedly, no degeneration occurs in the unmyelinated fibers [45]. These findings reveal that RSC are altered in CMT1A, but without any impact on the unmyelinated fibers, in comparison to the relation between myelinating SCs alteration and degenerated myelinated axons. Further studies need to elucidate the contribution of RSC to the pathogenesis of CMT1A.

2.2 Perisynaptic (terminal) Schwann cells (PSCs)

2.2.1 PSC phenotype and distribution

PSC, also known as teloglia or terminal Schwann cell, is a type of non-myelinating Schwann cell which is found above the presynaptic nerve terminal at the level of the NMJ. Louis-Antoine Ranvier described in 1878 the presence of a type of cell in the NMJ distinct from the axon terminal or the muscle fiber. He named this cells "arborization nuclei" because of their widespread projections along the NMJs. Later on, with improved histology techniques and in the era of electron microscopy, several studies identified the presence of this specific type of cell in the NMJ (**Figure 2C**).

PSCs express several markers that are used to highlight them in situ. The most common approach used is anti-S100b immunolabeling [46]. S100b is a nonspecific marker for all types of SCs, either myelinating or non-myelinating ones. In amphibians only, to distinguish PSCs from myelinating SCs, two specific antibodies are used, peanut agglutinin (PNA) [47] and 2A12 monoclonal antibody [48], which mark the extracellular matrix and the cells' surface, respectively. Interestingly, PSCs express several myelin proteins such as myelin-associated glycoprotein (MAG), galactocerebroside, protein zero (P0), and 2′,3′-cyclic nucleotide 3′-phosphodiesterase [49]. The cells are not involved in the process of myelination, though the presence of these proteins proves the common origin of the two types of Scs. Additionally, PSCs express on their surface several receptors such as acetylcholine receptors, ATP, purinergic receptors, and L-type voltage-dependent calcium channels that usually take part in the synaptic transmission [50–53] supporting the hypothesis that PSCs play an active role in the NMJ rather than having only a structural role.

Several studies determined that the number of PSCs gradually increase after birth [54]. Adult NMJ may contain one up to five PSCs [55–57], and their number is modulated by PSC-muscle cross talk through neurotrophins [58].

PSCs tend to be positioned at the presynaptic side, on top of the motor axon terminal, without the intervention of a basal lamina [55, 56]. Recently a new population of fibroblast-like cells named kranocytes—NMJ-capping cells—was detected on the other side, above the basal lamina of the PSC, covering all other cells of the NMJ. They are thought to have important roles in the NMJ repair after nerve injury [59, 60]. Kranocytes appear to communicate with PSCs via neuregulin signaling pathway to act synergistically after nerve damage [59].

Most studies about PSCs were performed either on amphibian (frog) or rodent (mouse) samples [53]. A peculiarity of the frog's NMJ, where the unmyelinated nerve terminal is completely surrounded by PSCs and does not form dilated terminal buttons and the synaptic contact is formed all along, is that PSCs send finger-like projections into the synaptic cleft, on the presynaptic side, which separate, at a regular distance, active areas where the neurotransmitters are released from covered areas [52, 61]. These active areas correspond on the opposite side to the folds of the sarcolemma, the postsynaptic element of the NMJ, which are rich in nicotinic acetylcholine receptors [52, 61]. In mammals, PSC projections do not reach the synaptic cleft (**Figure 2D**).

2.2.2 PSC roles in the formation and function of the neuromuscular junction

PSCs are involved in the growth and maintenance of the NMJ during development.

Although these cells do not take part in the initial formation of the axon-muscle junction, PSCs have key contributions in the next stages of NMJ development. In animal models lacking SCs, the axon reaches the muscle in the initial step of the NMJ formation, but only for a brief time [62, 63]. In the absence of SCs, the NMJ gets disrupted, suggesting the vital role of PSCs in the NMJ maintenance during development [64]. Soon after the contact between the axon and the muscle, PSCs intensively divide, sprout, and are primarily involved in the growth of the synapse [64].

PSCs are also involved in the physiological processes of polyneuronal innervation and synapse elimination. PSCs are involved in the multiple innervation process of the muscles and suffer a regression in parallel with the axonal withdrawal [1, 65, 66]. After the process of axonal withdrawal, PSCs are engaged in the removal of nerve debris, through phagocytosis [67].

The signaling pathway which facilitates the survival and growth of PSCs and the tight communication between PSCs and motor axons is the neuregulin1-ErbB pathway [1].

PSCs have important roles in the maintenance of the NMJ during the adult life as the structural support. Ablation in PSCs on the adult NMJ does not impede the immediate structure and function of the synapse, but after a period of time, the motor axon terminals retract, and the NMJ collapses [64, 68]. Thus PSCs have a significant contribution to the structural maintenance of the synapse under the action of physical factors such as the intense tractions between the nerve and the muscle [53].

These cells dynamically participate in the process of synaptic transmission of information between the motor axons and the muscles, having an important role in the modulation of NMJ activity [53, 57, 69]. Not only PSCs can alter the synaptic transmission, but PSC activity can also be modified by synaptic transmission. Or, as some authors like to say, PSCs can both "talk" and "listen" in the synapse [53, 69].

When the nerve terminal increases its firing rate and a large amount of neurotransmitter is released in the synaptic cleft, a simultaneous increase of intracellular calcium occurs in PSCs [70, 71]. A similar effect is obtained by applying exogenous acetylcholine and ATP, molecules normally released by the synaptic vesicles, to PSCs [51]. Moreover, the levels of intracellular calcium vary depending on the type of the nerve firing rate, either burst or continuous [72]. These events do not occur in the myelinating SCs and emphasize the detection of synaptic activity by PSCs and the modification of their cellular behavior secondary to the synaptic transmission [69]. This is similar to a decoding process of the synaptic activity. Thereby, the events correspond to the "listening" ability of PSCs in the synapse.

The increase of the PSC intracellular calcium levels does not play only a "decoder" role. This transient raising modulates the synapse by intensifying the neuromuscular transmission. PSCs are expressed on the surface of several G protein-coupled receptors with contributions in the modulation of the synapse activity [73]. Evidences suggest that different ligands of these G protein-coupled receptors determine different changes in the neuromuscular transmission, as follows: a GTP analogue decreased the neurotransmitter release, while a GDP analogue reduced the synaptic depression [73]. These events correspond to the "talking" ability of PSCs in the synapse.

Therefore, PSCs are not only a structural, passive component of the NMJ, but an active one. These evidences confirm that the NMJ is a tripartite synapse.

2.2.3 Roles in pathology

PSCs induce and guide the growth of nerve sprouts to re-establish the NMJ after nerve injury.

All the actions that PSCs perform in an attempt to regain the activity of the NMJ appear to be mediated by neuregulin1-ErbB signaling pathway [74].

First of all, after nerve degeneration, PSCs develop phagocytic traits for the clearance of the debris from the nerve terminals [75].

Second of all, PSCs are involved in the guiding of reinnervation. A few days after the nerve injury, PSCs from the altered NMJ begin to abundantly sprout, and these new processes reach adjacent undamaged synapses [76]. In this manner, "bridges" are established between the innervated and the dennervated NMJs. The role of the newly formed bridges is to facilitate the nerve pathway to find the altered NMJ and to regenerate the synapse more rapidly [69, 76]. However, satellite NMSCs seem to play a role in nerve regeneration after insult as well and might be involved in pathogenic pathways of neuropathic pain [77].

Miller Fisher syndrome is a Guillain-Barré syndrome variant with antibodies against GQ1b ganglioside that is clinically characterized by ataxia, ophthalmoplegia, and areflexia. Studies on mouse models revealed that PSCs represent an important target of the autoimmune process, the cellular destruction is complement dependent, and this pathogenic mechanism might be relevant for the human disease [68, 78].

Amyotrophic lateral sclerosis (ALS) is a challenge for both the clinician and the researcher due to the obscure pathological mechanisms that are still not completely understood. The role of glial cells in the pathophysiology of the disease is not clear yet. Most probably the SC modifications are a consequence of the neurodegeneration process. However in human patients with ALS, PSCs have abnormal features with cellular processes that extend into the synaptic cleft [79]. Additionally, in ALS mouse models, PSCs have abnormal intracellular levels of calcium, causing a flaw in the synaptic "decoding" function [80].

Another neuromuscular disease in which PSCs appear to be involved is spinal muscular atrophy (SMA). In an ultrastructural study on SMA mouse models, PSCs in the diaphragmatic muscle show changes in their morphology such as vacuole-like translucent profiles and an electron-dense cytoplasm [81]. Another study on SMA mouse models revealed that in the evolution of the disease, there is a progressive loss of PSCs, leading to an improperly remodeling and regeneration of the NMJ [82].

3. Conclusions

Although little is known on the NMSC, they are very important players for normal PNS function. Recent studies showed that RSCs play a very important role in the development of peripheral nerves and regeneration after injury. RSCs are also involved in the modulation of pain sensitivity in peripheral sensory neuropathies. Even in the absence of injury, disturbance in axonal-RSC interaction is followed by neuropathic pain.

Additionally, PSCs are mandatorily involved not only in synaptogenesis but also in the growth and maintenance of the normal synapse as well as after denervation. Morphological changes of PSCs were detected in various pathological conditions suggesting their potential involvement in the pathogenic mechanism of such diseases.

A better understanding of the molecular mechanisms that govern the development and functioning of NMSCs could broaden the perspective on the pathogenesis and potential therapeutic targets for neuropathy and peripheral nerve injuries.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

SCs	Schwann cells
RSC	Remak Schwann cells
NMSCs	nonmyelinated Schwann cells
NGF	nerve growth factor
GGF	glial growth factor
ERK	extracellular signal-regulated kinase
Nte	neuropathy target esterase
FGFR	fibroblast growth factor receptor
NRG1	neuregulin 1
Nrg1-III	neuregulin 1 type III
GDNF	glial cell line-derived neurotrophic factor
GABBR1	gamma-aminobutyric acid type B1 receptor
SCP	SC precursors
iSch	immature Schwann cells

PSCs	perisynaptic Schwann cells
NMJ	neuromuscular junction
PNA	peanut agglutinin
ALS	amyotrophic lateral sclerosis
CMT1A	Charcot-Marie-Tooth type 1A

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Chapter 5

Recurrence of Guillain Barré Syndrome in Patient Pediatric with Presentation of Two Different Clinical Variants

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Abstract

Guillain Barré Syndrome (GBS) is an acute demyelinating polyradiculoneuropathy, with unusual heterogeneous clinical variants in pediatrics. There may be infection prior to the clinical manifestations of GBS. Establishing a diagnosis and treatment is challenging. In the present work, a 7 year old schoolgirl is presented, healthy, without risk factors, with recurrence on 2 occasions with different clinical variants of GBS. The 1st episode of GBS was 2 years old, with a history of respiratory infection. Debuting later with clinical manifestations of acute inflammatory demyelinating variant GBS. During her hospital stay, she received treatment with intravenous immunoglobulin (IVIG) (dose of 1grkg for 2 days), without respiratory and/or bulbar compromise, being discharged and sent to rehabilitation to continue multidisciplinary management. The 2nd episode of GBS was at 7 years, I presented recurrence of acute axonal motor variant GBS, secondary to respiratory infection, with acute evolution and respiratory failure, bulbar involvement, areflexia and dysautonomias, requiring mechanical ventilation for 37 days, administering IVIG of 1 grkg for 2 days). During the hospital course there was a serious neurological condition, with gradual improvement, discharging with a tracheostomy, without supplemental oxygen, tolerating the oral route and sent to neurological rehabilitation and otorhinolaryngology to reduce subsequent sequelae.

Keywords: Guillain Barré syndrome, Acute demyelinating variant, axonal motor variant, recurrence Electrophysiological studies

1. Introduction

Guillain Barré Syndrome (GBS) is an acute demyelinating polyradiculoneuropathy, of autoimmune origin, which presents with various heterogeneous clinical variants [1]. In most cases there is an infectious picture prior to the clinical manifestations of GBS (acute paralysis, weak limbs and inability to ambulation) [1, 2].

In 1857, Landry described the first cases of GBS. The affected patients presented with predominantly ascending motor paralysis, respiratory failure and death [3, 4]. In 1916, Guillain - Barré Strol [4] demonstrated that these patients presented motor deficits and areflexia, but without sensory affection and with albuminocytological dissociation as part of the integral diagnosis of the SGB [4].

In 1990, Asbury and Comblath established the electrodiagnostic criteria for GBS, characterized by a delay in the conduction velocity of two or more motor nerves [5].

At present, GBS is the most frequent cause of flaccid paralysis in previously healthy children [6]. Worldwide, the annual incidence is 0.6 to 2.4 cases per 100,000 inhabitants, in any age group, affecting both genders with an H relationship./M 1.5: 1 [7].

The main infectious agent reported in outbreaks of GBS is C. jejuni [8]. Other infections associated with GBS are: cytomegalovirus (CMV), Epstein–Barr virus, Influenza A virus, Mycoplasma pneumoniae and Haemophilus influenzae [9].

GBS is defined clinically, pathologically, and electrophysiologically as an acute inflammatory demyelinating polyneuropathy. According to the characteristics of the nerve conduction studies, it was observed that GBS is characterized by; slowing of conduction speeds, conduction block, delayed latencies and/or scattered responses; but over time, the evidence from several studies indicated that there are different clinical, serological, and electrophysiological characteristics in each of the GBS variants.

The following describes in detail the pathophysiology and clinical picture that characterizes each of the GBS variants:

a. In the variant of the Acute Inflammatory Demyelinating type (PDIA); there is involvement of the motor roots [10], segmental demyelination, infiltration of mononuclear cells, predominantly T lymphocytes and macrophages in the peripheral nervous system, chains of sympathetic ganglia and cranial nerves [11]. In addition to proliferation of Schwann cells as part of the repair mechanism. There is an antibody cross-reaction against ganglioside GM1, finding axonal epitopes similar to gangliosides present in Campylobacter jejuni (serotypes 019 and 041), whose polysaccharides are similar to gangliosides located in the nerve, this being the explanation for direct axonal damage and demyelination [12]. The main symptom is symmetrical weakness in the lower extremities, decreased or absent deep tendon reflexes (areflexia) and localized pain in the lower extremities or low back pain, present in 79% of the reported trials [13].

b. In the Miller Fisher Syndrome (SMF) type variant; the clinical findings are very similar to those present in Acute Inflammatory Demyelinating. The main culprit is ganglioside GQ1b [14], located in the myelin of cranial nerves, the main ganglioside damaged by specific cross-reactive antibodies caused by Campylobacter jejuni infections. The ganglioside GQ1b is considered a marker of ophthalmoplegia in GBS [15, 16]. The anti-GT1 antibody is also a marker of compromise and translates bulbar cranial nerve damage in GBS [17]. The classic triad of MFS is: ataxia, areflexia and ophthalmoplegia. About 50% of the cases have been reported as the first clinical condition diplopia and/or facial paresis. In the case of external ophthalmoplegia very characteristic of SMF, the first muscle affected is the superior rectus muscle, followed secondarily by lateral rectus muscle paralysis and finally the inferior rectus muscle is affected. Bell's phenomenon is common in patients with MFS [18].

c. In the Axonal type variant; no inflammatory changes are seen, only a discrete primary lesion is found at the level of the nodes of Ranvier, explaining the axonal degeneration. The anti-GD1a antibody is specific for this variant [19].

The clinical picture is not severe and depends on the extent of axonal injury. Regarding the clinical examination of the patient, the tendon reflexes are preserved and he may even have hyperreflexia. Distal limb involvement shows rapid and complete recovery [18, 20]. Therefore, regardless of GBS variants, axons are the main target for autoimmune injury [21].

Regarding medical treatment, the effect of immunotherapy in GBS has been studied for many years (mainly in studies of randomized controlled trials), establishing that the use of intravenous immunoglobulin (IVIG) and plasma exchange (plasmapheresis) they are effective [22]. The cornerstone of GBS treatment in pediatric patients is based on the use of intravenous immunoglobulin. The treatment can be applied in 2 different therapies; 1st therapeutic (most effective): immunoglobulin dose (2 gr/kg of body weight) administered in two days at 1 gr/kg per day. The 2nd therapy: dose of immunoglobulin at 0.4 gr/kg of body weight administered in 5 days [2, 23].

The specific indications for the use of IVIG in GBS are; rapid progression of muscle weakness, respiratory failure or ventilatory mechanical support, involvement of the bulbar or cranial nerve and inability to ambulation [2]. Plasmapheresis has shown the same efficacy as immunoglobulin but constitutes a more invasive treatment, being reserved only for cases of intolerance or poor response to intravenous immunoglobulin administration [24].

The severity of the clinical picture is important as a prognostic factor in GBS. About 40% of affected children have an inability to ambulate during the acute phase. In severe cases, approximately 25% of patients will require special supports in Intensive Care Units due to the need for support with artificial ventilation secondary to dysautonomias [12, 25–27].

The authors present the case of a 7 year old girl with severe and atypical Guillain Barré syndrome, describing the clinical course and associated complications in a recurrence of GBS in pediatrics.

2. Presentation of clinical case

7 year old female. Healthy mother and father. No hereditary diseases. Surgical, traumatic, transfusion, allergic, rash history questioned and denied. Complete vaccination schedule according to age.

3. Hospitalizations

3.1 1st hospitalization

At 2 years of age due to acute inflammatory demyelinating variant Guillain Barré syndrome. In September 2012, GBS was diagnosed secondary to an upper respiratory tract infection 1 week prior to admission, with partial improvement in infection after administration of antimicrobials and antipyretics for 3 days. Later clinical symptoms of GBS characterized by weakness in both lower extremities were added, going to the emergency room. Upon admission to the emergency room, she found normal vital signs; HR 116/minute, FR 30/minute, Temp 36 °C, oxygen saturation 93%. Physical examination: female of apparent age similar to chronological age, adequate hydration, normocephalic skull, oral cavity with grade II tonsillar hypertrophy and hyperemic pharynx, neck without megalia, cardiopulmonary without compromise, soft abdomen without megaly or peritoneal irritation, upper extremities; eutrophic, conserved strength 5/5 on the Daniels scale, conserved tendon

reflexes, pain withdrawal and conserved sensitivity, lower extremities; eutrophic, strength reduction 3/5 on the Daniels scale, bilateral areflexia, withdrawal to pain and preserved sensitivity. Neurological: awake, reactive to external stimuli, non-measurable gait, preserved sensitivity, preserved cranial nerves, absent meningeal signs, no neurological deterioration or dysautonomias.

3.1.1 Hospital clinical evolution

Day 1. Laboratories. Hematic biometry: leukocytes 6,800 leu/µl, neutrophils 27%, lymphocytes 62%, monocytes 8%, hemoglobin 13.6%, hematocrit 40.3%, platelets 482 thousand, CRP 0 mg/dl, CPK 737 U/l. Seric electrolytes: sodium 138 meq/l, potassium 4.9 meq/l, chlorine 105 meq/l, calcium 11.1 mg/dl, phosphorus 6.2 mg/dl, magnesium 2.3 mg/dl. Blood chemistry and kidney function tests: glucose 70 mg/dL, BUN 22 mg/dL, Urea 47 mg/dL, creatinine 0.3 mg/dl. Lumbar puncture: clear, colorless, transparent liquid, 1 cells, 100% monocytes, negative erythrocytes, glucose 43 mg/dl, chloride 118.3 meq/L, proteins 57 mg/dl, pandy positive (+), pH 7.6, lactate 1.6, no bacteria, negative coagglutination. Medical treatment was started with intravenous immunoglobulin (IVIG) at a dose of 1 gr/kg for 3 days.

Day 2. Neuroconduction study: acute inflammatory demyelinating variant GBS (see **Figure 1**).

Day 3. Negative cerebrospinal fluid culture. Negative peripheral blood culture.

Day 6. During his hospital stay, he presented adequate evolution, with gradual improvement in the mobility of the lower extremities; strength 4/5, bilateral areflexia, preserved sensitivity, no secondary complications, tolerating the oral route, no respiratory distress, without requiring ventilatory support, deciding his discharge with wheelchair support and sent to pediatric rehabilitation for 6 months with clinical improvement.

3.2 2nd hospitalization

7 year old female. Condition: 3 day history of upper airway infection with torpid evolution despite established medical treatment, adding paresthesias of the lower limbs with ascending, progressive and symmetrical spread, extending to the upper limbs and poor management of bronchial secretions, therefore which, goes to the emergency service for assessment. Upon admission to the emergency service, she had stable vital signs; HR 95/minute, FR 14/minute, oxygen saturation 93%, temperature 36.5 °C. Physical examination: female of apparent age similar to the chronological one, adequate hydric status, full oral cavity without alterations, neck without megaly, cardiopulmonary without compromise, abdomen without megaly, no data of peritoneal irritation, upper extremities; eutrophic, strength decreased 1/5 on the Daniels scale in the left upper limb and 2/5 in the left upper limb, bone tendon reflexes abolished and sensitivity preserved, lower limbs; eutrophic, decrease in strength 0/5 on the Daniels scale, bilateral areflexia, non-withdrawal of pain and preserved sensitivity. Neurological: awake, reactive to external stimuli, no palpebral ptosis, normoreflectic isochoric pupils, normal bilateral fundus, preserved cranial nerves, preserved superior mental functions, non-assessable gait, non-assessable romberg signs, preserved sensitivity, absent meningeal signs, no dysautonomias.

Guillain Barré Syndrome was diagnosed, for which it was decided to prescribe hydroelectrolytic treatment with solutions to basal requirements by the Hollidey-Sigar formula.

Motor Nerve Study

Left Median Nerve

Rec Site: ADM Stim Site	Dur (ms)	Amp (mV)	Area (mVms)	Dist (mm)	C.V. (m/s)
Wrist left	5.3	.217	0.5		
B. Elbow	4.9	.167	0.5	100	36.4

Right Tibial Nerve

Rec Site: AH Stim Site	Dur (ms)	Amp (mV)	Area (mVms)	Dist (mm)	C.V. (m/s)
Ancle right	0.0	0	1.7		
Pop. Fos.	0.0	0	0.6		

Left Tibial Nerve

Rec Site: AH Stim Site	Dur (ms)	Amp (mV)	Area (mVms)	Dist (mm)	C.V. (m/s)
Ancle left	0.0	0	1.8		
Pop. Fos.	0.0	0	0.0		

Sensory Nerve Study.

Left Median Nerve

Rec Site: Wrist Stim Site	Lat (ms)	Pk Lat (ms)	Amp (uV)	Dist (mm)	C.V. (m/s)
5th dig	1.9	2.3	103.3	60	31.6
5th dig	1.9	2.3	102.5		

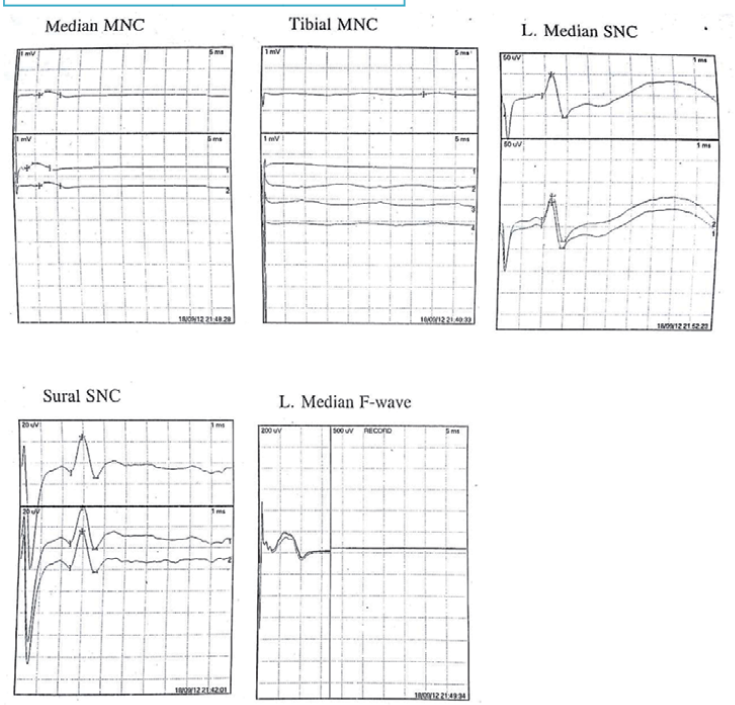
Right Sural Nerve

Rec Site: Ankle Stim Site	Lat (ms)	Pk (ms)	Lat	Amp (uV)	Dist (mm)	C.V. (m/s)
Mid calf r	2.4	3.0		39	90	37.5
Mid calf r	2.4	3.0		38.3		

F-Wave Study

Left Median Nerve

Rec Site: ADM Stim Site: Wrist	Latency (ms)	Amplitude (mV)
M wave	4.5	0.15
F wave	NR	1.50



Interpretation. Neuroconduction study with abnormal response, distal and proximal peripheral nerve with delayed conduction compatible with acute inflammatory demyelinating variant GBS.

Figure 1.
Neuroconduction study (female 2 years).

3.2.1 Hospital clinical evolution

Day 1. During her first hours in the emergency service, she presented acute respiratory distress, which is why advanced management of the airway was decided and she was admitted to the Intensive Care service, starting an infusion of Midazolam at 100 mcgkghr. Laboratories Hematic biometrics: leukocytes 14,140 leu/μl, neutrophils 59.6%, lymphocytes 29.7%, hemoglobin 14.8%, hematocrit 44.2%, platelets 434 thousand, ESR 20 mm/h, PCT <0.5 ng/ml, CRP <0.5 mg/L. Liver function tests: BT 0.37 mg/dl, BD 0.11 mg/dl, BI 0.26 mg/dl, TGO 34 IU/L, TGP 21 IU/L, GGT 9 IU/L, CK 28.9 IU/L, CK-MB 28 IU/L. Blood chemistry and kidney function tests: glucose 96 mg/dL, urea 34 mg/dL, BUN 16 mg/dL, creatinine 0.38 mg/dL.

Pediatric Neurology Assessment. Neurological examination with patient under sedation with hyporeflexic isochoric pupils, with a tendency to miosis, facial symmetry, motor with force in the upper extremities proximal 2/5 and distal 1/5 (assessed prior to sedation), lower extremities proximal force and distal 0/5 REM triceps and biceps decreased, bilateral absent patellar and achilleum, non-clonus flexor plantar response, preserved sensitivity, pain withdrawal, rest apparently normal. Patient with clinical evolution of GBS with rapid progression to compromise at the level of the respiratory and bulbar muscles as a poor prognostic factor, therefore, it was decided to start intravenous immunoglobulin at a dose of 1 grkg for 2 days. Lumbar puncture: clear, colorless, transparent liquid, 2 cells, 60% monocytes, negative erythrocytes, glucose 54 mg/dL, chloride 110 meq/L, proteins 103 mg/dL, pandy positive (+), pH 7.6, lactate 1.4, no bacteria, negative coagglutination. Simple and contrasted CT of the skull: without structural alterations and/or abnormal reinforcements. Chest X-ray: no bone structural alterations, no atelectasis, consolidation or pneumothorax.

Day 2. During her 2nd day, she presented a quantified fever>38 degrees Celsius with previous laboratories within normal parameters, but antimicrobial therapy was decided with a double antimicrobial scheme with Cefotaxime and Vancomycin. Neuroconduction study is requested. Study report: abnormal suggestive of GBS with axonal component (see **Figure 2**). After obtaining a neuroconduction study, medical treatment was started with intravenous immunoglobulin (IVIG) at a dose of 1 gr/kg for 2 days.

Day 7. For 7 days in the intensive care service, she was maintained with ventilatory mechanical support with orotracheal intubation, with poor clinical motor evolution and absence of spontaneous respiratory movements as well as protective reflexes of the airway, therefore, due to the condition neurological, it was decided to perform a tracheostomy to avoid subsequent complications.

Day 8. Sedation based on Midazolam is withdrawn, and analgesic treatment with Ketorolac and paracetamol is continued, without complications.

Day 11. Patient establishes poor verbal communication and begins oral intake based on clear liquids with adequate tolerance. Cough reflex absent.

Day 17. Concludes double antimicrobial regimen with Cefotaxime and Vancomycin (15-day regimen).

Day 19. Progression of oral feeding with a polymeric diet and later a soft diet with adequate tolerance.

Day 23. Food based on a normal diet without eventualities. Gradual evolution with clinical improvement in mobility of the right upper limb and shoulder girdle.

Day 33. Increased mobility of the right hand, left hand, feet in dorsoflexion, and pronosupination.

Day 38. Increased mobility of the bilateral shoulder girdle and hip.

Motor Driving

Bilateral Peroneal Nerve

	Right tibial	Left tibial	Right middle	Left middle
Latencies	7.1 ms	7.7 ms	3.8 – 8.7 ms	Not valued
Amplitude	0.1 Mv	0.5 mV	0.1 Mv	
Speed			37 m/s	

Sensitive Driving

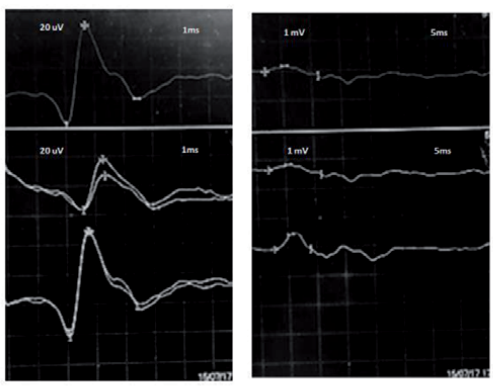
Bilateral Sural Nerve

	Sural right	Sural left
Latencies	2.2 ms	2.4 ms
Amplitude	51 uV	46 uV
Speed	45 m/s	42 m/s

Wave f

Bilateral Posterior Tibial Nerve

	Right tibial	Left tibial
Latencies	Not obtained	Not obtained
Recruitment		



Interpretation. Study of motor neuroconduction of the peroneal nerve without obtaining a response. Prolonged distal tibial nerve latency, low amplitude, and temporal dispersion. Median nerve motor response decreased in amplitude and delay in conduction with similar response dispersion. Wave F not obtained. The sensitive response is only preserved with the presence of a delay in its conduction. GBS with axonal component

Figure 2.
Neuroconduction study (female 7 years old).

Day 39. Female patient who deserved mechanical ventilatory support for 39 days, progressing with gradual clinical improvement, deciding on a programmed withdrawal of the ventilator without complications, continuing with medical treatment with pulmonary physiotherapy, gentle aspiration of secretions if necessary and supplemental oxygen support, with no evidence of respiratory distress.

Day 40 - Day 43. Multidisciplinary treatment with neurological and pulmonary rehabilitation, education to a family support network for management and care of tracheostomy. Neurological examination: favorable evolution, strength 2/5 on the Daniels scale in the upper extremities, strength 0/5 on the Daniels scale in the lower extremities (Hughes IV Scale - patient confined to bed or chair without the ability to walk), no compromise respiratory, preserved brain stem reflexes. Laboratories: results are collected as part of the GBS protocol in pediatric patients with IgM AC. Anti - Helicobacter Pylori, negative report.

Patient who presented gradual clinical improvement, which is why he was discharged home with a tracheostomy, without supplemental oxygen, tolerating oral route. It is sent for evaluation and follow-up by the neurological rehabilitation and otorhinolaryngology service for medical follow-up due to underlying pathology.

4. Discussion

The recurrence of GBS in pediatrics is rare, as well as the presentation of two clinical variants, which presented different clinical course and remission, despite receiving adequate treatment with intravenous immunoglobulin at a dose of 1 grkg. As previously mentioned, during the 1st episode with acute inflammatory demyelinating variant GBS, the patient presented remission of clinical symptoms without respiratory compromise. But this is not the same way in the 2nd episode of GBS, acute axonal motor variant, where it progresses with acute, torpid neurological evolution, with respiratory and bulbar involvement, meriting phase III ventilation and tracheostomy programming as a protective measure of airway and deficit motor in all 4 extremities for 5 weeks with gradual improvement. Upon discharge, the patient with great limitation to daily activities, staged according to the Hughes Scale in grade IV, found herself confined to bed and requiring the use of a wheelchair to perform daily activities, due to the involvement and motor involvement in the extremities lower, continuing with neurological rehabilitation to delimit the severity of the sequelae.

At present, it is rare to find a case of RGBS, this case being one of the few presentations with an axonal phenotype in a child.

Therefore, it is important for clinicians to recognize the various features of RBGS in recurrence [28].

Remembering that patients may present similar symptoms, but have different findings in the examination, clinical course and electrodiagnostic studies [28, 29].

RGBS may be an underdiagnosed and underrecognized entity in pediatric patients that deserves further study with regard to epidemiology and pathophysiology.

5. Conclusion

Guillain Barre syndrome is a neurological disease that occurs favorably in most cases, but there are clinical variants that can be life threatening, being considered an

emergency in pediatrics. The case report shows the importance of the clinical correlation and neuroconduction study to confirm the diagnosis of GBS at an early stage, allowing in turn to initiate the ideal treatment with intravenous immunoglobulin (IVIG) in a timely manner (especially in the most severe GBS), as established in the international guidelines for the diagnosis and treatment of GBS. As established in the literature, mortality from GBS corresponds to less than 5% of cases, but there is a close increase between 15–30% in patients requiring mechanical ventilation. The clinical course of GBS in pediatrics turns out to be more favorable and benign compared to that in adults. Remember that avoiding the mostly associated clinical complications (pneumonia, sepsis, pulmonary embolism, respiratory paralysis, dysautonomias) influence the prognosis of GBS.

Carrying out a prevention and control of possible hospital infections during the evolution of GBS, through adequate care of the airway, conscious use of antibiotics, strict and continuous monitoring, will allow to delimit the sequelae and subsequent complications due to the underlying pathology, making emphasis on physical rehabilitation therapy and adequate nutritional intake.

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Section 3

Peripheral Neuropathies

Chapter 6

Diabetic Peripheral Neuropathy

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Abstract

Diabetes mellitus is one of the most common medical disorders often associated with neurological complications. Peripheral neuropathy is the most common neurological complication from diabetes with a prevalence of 10–26% of newly diagnosed adult diabetics. Diabetic neuropathy is a heterogeneous group of conditions that present with sensory and/or motor and/or autonomic dysfunction and affect different parts of the peripheral nervous system. Diabetic neuropathy might present as a polyneuropathy, mononeuropathy, mononeuropathy multiplex, radiculopathy, and/or plexopathy. Diabetic neuropathies may also be associated with foot ulcers and infections in 5–24% of patients, which translate into five out of 1000 of diabetics ending with an amputation. Therefore, it is essential to screen diabetic patients for early recognition and management of diabetic neuropathies.

Keywords: diabetic peripheral neuropathy, screening, management

1. Introduction

Peripheral neuropathies (PNPs) encompass a large group of disorders of different etiologies that may present with sensory and/or motor deficits and/or autonomic dysfunction depending on the predominant nerve fiber being affected. They are common disorders linked to severe impairment and poor prognosis [1]. PNPs cause loss of sensation, and the risk of feet ulceration may lead to infections. Loss of protective sensation is the first sign and when identified must be followed with the appropriate preventive measures. Peripheral neuropathy is a complication seen in approximately 50% of patients with diabetes, but up to 50% of patients with peripheral neuropathy may be asymptomatic [2, 3].

Peripheral neuropathies may result from a broad spectrum of diseases including diabetes, toxic exposures such as alcohol and chemotherapy; immune-mediated conditions and gene mutations. Neuropathies are very common disorders with an incidence of 77/100,000 inhabitants per year and a prevalence of 1–12% in all age groups and up to 30% in older people [4–7].

One of the most common worldwide chronic diseases is diabetes mellitus (DM). According to the International Diabetes Federation (IDF), DM affects 425 million people worldwide, and for the year 2045, this figure is projected to rise to 628 million [8]. Increasing prevalence of diabetes type 1 and type 2 results in an increase of diabetes-related complications, which conversely impact the quality of life (QoL) [9].

2. Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is the most common long-term complication of diabetes and the primary cause of foot ulcers and lower-extremity amputation. Diabetic peripheral neuropathy has significant impact on the quality of life. It may present with the typical feet involvement to a more wide range of symptoms and signs from myelopathy-like to a myopathy-like symptoms to even death. Diabetic neuropathy affects between 23 and 76% of people [10]. The progression of DPN is related to poor glycemic control, aging, long diabetes duration, visceral obesity, hypertension, smoking, hyperinsulinemia, and dyslipidemia [11]. Improved glycemic control, early detection, and preventive care can avoid adverse outcomes.

DPN is a well-known microvascular complication of type 2 diabetes mellitus resulting from chronic hyperglycemia and defined by a peripheral nerve dysfunction in a diabetic patient after other etiologies have been excluded. Neuropathy develops in about 5–10% of diabetic patients in the first year, and 60–70% of diabetic patients experience some type of diabetic peripheral neuropathy after 20 years of duration of diabetes [12, 13].

2.1 Pathogenetic mechanisms

Peripheral nerve damage in diabetic peripheral neuropathy is caused by a variety of mechanisms; the most important are oxidative stress, inflammation, and mitochondrial dysfunction. Diabetes activates inflammatory molecules, causing a functional nitric monoxide deficit, activation of alternative metabolic pathways, accumulation of glycation end products, oxidative stress, and inflammation. The expression of pro-inflammatory cytokines including C-reactive protein, TNF-, and IL-6 is higher in people with diabetes. Chronic hyperglycemia causes cytokines to infiltrate vascular tissue, which will reduce the body's ability to heal by its own [14].

Chronic hyperglycemia stimulates macrophages, such as cells secrete TNF-, resulting in an increased of cytokine released. TNF- boosts the expression of endothelial cell adhesion molecules, precipitating atherosclerosis. In patients with poorly regulated diabetes, increased TNF development as a result of hyperglycemia is a factor in exacerbating insulin resistance. The effect of TNF- on Schwann cells also explains local demyelination in peripheral neuropathy [15].

Hyperglycemia primarily affects Schwann cells, resulting in cell damage, altered axon integrity, and impaired growth factor signaling [16–18]. Defective inflammatory pathways in axons and Schwann cells, including advanced glycation end product/receptor (AGE/RAGE) signaling, have been observed in diabetic neuropathy in animal models that lead to nerve damage [19].

Sensory neurodegeneration in the chronic stage of diabetes was linked to early damage to the distal axons of both upper and lower limb neurons in a study involving both human and animal models, revealing a pattern that explains the glove and stocking distribution loss of sensation seen in DPN. These changes are accompanied by widespread defects in electrophysiology and gene expression, all of which contribute to a degenerative phenotype [20]. Existing data about the development of DPN, such as increased oxidative and nitric oxide stress, polyol accumulation, microangiopathy, abnormal AGE-RAGE signaling, and/or mitochondrial dysfunction, account for a variety of mRNA modification that modify miRNA expression patterns, resulting in a wide range of DPN phenotypes.

Endothelial nitric oxide synthase (eNOS) dysfunction can play a key role in the pathogenic pathway that leads to diabetic vascular complications, such as DPN. As a result, eNOS is thought to be a potential cause for DPN progression.

Hyperglycemia is associated with defects in the vasa nervorum and nerve fiber loss in the early stages of DPN. The ischemia and hypoxia in the nerves of patients with type 2 diabetes mellitus due to microangiopathy of vasa nervorum have always been observed and possibly a pathogenic mechanism of DPN [21–23].

2.2 Clinical manifestations

Diabetes can damage different parts of the peripheral nervous system with distal symmetric polyneuropathy (DSP) being the most common presentation. The symptoms are symmetric and with predominant sensory symptoms over motor involvement. Sensory symptoms such as numbness, tingling, and pain are common in DSP patients. These characteristics begin in the feet and spread proximally in a length-dependent pattern known as stocking-and-glove distribution [24]. Other patterns of injury include small-fiber predominant neuropathy, radiculo-plexopathy and autonomic neuropathy, among others.

DSP has an effect on the physical and emotional well-being of patients. Sensory loss caused by DSP often causes trouble walking, which can lead to falls. DSP is one of major risk factors for falls in diabetic patients along with retinopathy and vestibular dysfunction. Diabetic DSP patients are 2–3 times more likely than diabetics without neuropathy to fall. Diabetes is the leading cause of lower extremity amputations, with a 15-fold increase in the likelihood of this life-changing complication. Moreover, 80,000 lower extremity amputations are performed each year in patients with diabetes [25–27].

Neurogenic pain, numbness, a lack of control of voluntary movements, and a susceptibility to foot ulceration that contributes to infections and toe or foot amputations are all signs of diabetic neuropathy. Diabetic patients have a 15-fold higher risk of toe or foot amputations than nondiabetic patients [28].

According to Toronto Consensus Panel on Diabetic Neuropathy, DPN is defined as a symmetrical, length-dependent sensorimotor polyneuropathy that develops in the background of long-standing hyperglycemia, associated de-arrangements, and cardiovascular risk factors [29]. Different studies reported that some patients with prediabetes develop neuropathic complications, whereas others reported little evidence of neuropathy even after long-standing diabetes. This observation confirms the involvement of genetic etiological factors associated with the development of DPN [30].

Neuropathic pain is one of the major disabling symptoms of patients with DSP. It is estimated that diabetic neuropathic pain (DNP) develops in 10–20% of the diabetic population overall and can be found in 40–60% with documented neuropathy. Like other types of neuropathic pain, DNP is characterized by burning, electric, and stabbing sensations with or without numbness [31–33]. It is characteristically more severe at night often resulting in sleep disturbance. Together with painful symptoms during the day, this often leads to a reduction in quality of life. In one study, the burden of painful DPN was reported to be significant, resulting in persistent discomfort following polypharmacy and high resource usage, as well as limitations in everyday activities and dissatisfaction with treatments that were frequently deemed ineffective. DPN that is chronic, persistently painful, and highly distressing is linked to severe depression, anxiety, and sleep loss [34, 35]. Other types of diabetic neuropathies includes small-fiber polyneuropathy, mononeuropathy, mononeuropathy multiplex, radiculopathy, plexopathy (diabetic amyotrophy), autonomic neuropathy, and treatment-induced neuropathy.

3. Screening or diagnostic assessment

A staging system, which has four stages, was used to provide a framework for diagnosis and management for DPN (**Table 1**) [36].

Stage of diabetic peripheral neuropathy		Characteristics
Stages 0/1	No clinical neuropathy	Asymptomatic
Stage 2	Chronic painful	Positive symptomatology nocturnal pain, burning, shooting, stabbing pains ± pins, and needles
		It may have absent sensation to several modalities and reduced or absent reflexes
	Acute painful	Less common
		It may be associated with initiation of glycemic therapy in poorly control diabetes
		Normal or minor sensory features in the peripheral neurological examination
	Painless with complete/ partial sensory loss	No symptoms or numbness/deadness of feet; reduced thermal sensitivity; painless injury
		Signs of reduced or absent sensation with absent of reflexes
Stage 3	Late complications of clinical neuropathy	Foot lesions, e.g., ulcers
		Neuropathic deformity, e.g., Charcot joint
		Nontraumatic amputation

Table 1.
The staging system of diabetic peripheral neuropathy.

The prevalence of neuropathy is determined by subjective complaints, signs, or nerve conduction studies. Electrodiagnostic findings provide a higher level of specificity for the diagnosis of polyneuropathy and should be included as a part of the assessment. Nerve conduction studies (NCSs) are the most informative part of electrodiagnostic evaluation, which commonly includes both NCS and needle electromyography. NCSs have been a criterion or gold standard test for confirming the diagnosis of peripheral neuropathies.

A simplified scoring system, the Diabetic Neuropathy Symptom Score (DNS), assesses pain, numbness, tingling, and ataxia. The maximum score of DNS is four points, one point or more indicates neurological abnormalities [37–39]. To quantify clinical neuropathy, the Neuropathy Symptom Profile, the Neuropathy Symptom Score, and the Neuropathy Disability Score were developed. The Michigan Neuropathy Rating Scale consists of two parts. The first part is the Neuropathy Screening Instrument, which consists of a 15-item questionnaire on foot sensation, including numbness, burning, and sensitivity. The second part is the Diabetic Neuropathy Score, which consists of clinical neurological examination and nerve conduction studies. Sensation, including vibration, pin prick, and light touch; distal muscle strength; and reflexes (biceps, triceps, quadriceps femoris, and Achilles) are assessed [40].

The performance of the protective sensation of the foot in diabetic patients is monitored using a variety of instruments. Pain perception, vibration perception, temperature perception, and deep reflexes are some of the most popular screening methods for DPN. Monofilaments, such as Semmes-Weinstein Monofilament Testing (SWMT), are one of the safest and most cost-effective ways to screen DPNs. SWMT is calibrated to the point that if a force of 10 g is applied to the point where the monofilament bends, but the patient does not notice it, that point is deemed insensate. This is a basic test that predicts the likelihood of foot ulceration in diabetic patients. To assess the presence of sensation, certain points on the feet are

stimulated by placing monofilament on the skin. It has a high sensitivity for detecting the possibility of foot ulceration and helps to prevent traumatic injuries [41–43].

In order to assess pain, several scales are used. Most common and oldest is the Numerical Pain Rating Scale, which is an 11-point Likert scale (0 = no pain to 10 = worst possible pain). Other validated scales such as Neuropathic Pain Symptom Inventory [44], Modified Brief Pain Inventory [45], neuropathic pain questionnaire [46], the LANNS pain scale [47], and McGill Pain Questionnaire [48] are often used.

Quality of life (QoL) might be assessed with neuropathy-specific instruments that are based on patient's experience of neuropathic pain, such as NeuroQoL [49], Norfolk Quality of Life Scale [50], and Neuropathic Pain Impact on Quality of Life Questionnaire (NePIQoL) [51]. The impact of painful symptomatology on mood can be evaluated using scales such as Hospital Anxiety and Depression Scale (HADS) [52].

The other scoring systems such as Clinical Neurological Examination (CNE), Diabetic Neuropathy Examination (DNE), Diabetic Neuropathy Symptom score (DNS), Michigan Neuropathy Screening Instrument (MNSI), Neuropathy Disability Score (NDS), Neuropathy Impairment Score (NIS), Neuropathy Impairment Score in the Lower Limbs (NIS-LL), Neuropathy Symptom Profile (NSP), Neuropathy Symptom Score (NSS), Toronto Clinical Scoring System (TCSS) can be used to screen and determine the severity of DPN [39]. Clinical care guidelines have recommended that annual screening for peripheral neuropathy occurs in all patients with diabetes, as part of routine evaluation to prevent complications.

Routine NCSs include evaluation of motor function of the median, ulnar, peroneal and tibial nerves and sensory function of median, ulnar, radial, and sural nerves. Different nerves attributes such as amplitudes are used in the assessment of axonal status; and latencies, conduction velocities, and F-waves latencies as function of myelination. Amplitudes are reduced in axonal damaged. In demyelinating neuropathies, nerve conduction latencies and F-waves latencies are prolonged and conduction velocities are reduced.

4. Management

Clinicians face a significant challenge in assessing and treating DPN, and an empathic and multidisciplinary approach is essential because the effect of painful DPN is varied and multidimensional. Ideally, a multidisciplinary team might include input from nutritionists, endocrinologists, neurologists, pain specialists, nurse practitioners, podiatrists, psychologists, physiotherapists, and others [53].

There is a general consensus that good blood glucose control should be the first step in the management of any form of diabetic neuropathy. Hypertension and hyperlipidemia, which are risk factors of large vessel diseases, are also commonly seen in DPN, and it is also important to address them.

Some of the commonly prescribed treatments include physiological glucose control (HbA_{1C} 6–7%), along with lifestyle modifications (i.e. diet, exercise). Tricyclic antidepressants (TCAs) such as amitriptyline and imipramine promote successful analgesia to thermal, mechanic, and electrical stimuli in diabetic patients by the inhibition of noradrenalin and/or serotonin reuptake synapses of central descending pain-controlled systems. Serotonin and noradrenalin reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine relieve pain by increasing the synaptic availability of 5-hydroxytryptamine and noradrenaline in the descending inhibitory pathway

against pain. The two anticonvulsants most commonly used to treat neuropathic pain are gabapentin and pregabalin, which bind to the α-2-δ subunit of the calcium channel, reducing calcium influx and thereby resulting in decreased synaptic neurotransmitter release into the hyperexcited neuron [54–56].

According to the European Federation of Neurological Societies' recommendations, first-line therapies could include TCAs, SNRIs, gabapentin, or pregabalin. The National Institute for Health and Clinical Excellence in the United Kingdom recently released recommendations on the treatment of neuropathic pain in non-specialist settings, which included a section on painful DPN management. Despite the fact that the level of evidence for pain effects with duloxetine, pregabalin, and gabapentin is comparable, the National Institute for Health and Clinical Excellence recommends that oral duloxetine be used first, with amitriptyline as an alternative and pregabalin as a second-line treatment [57–59].

There are wide ranges of alternative therapies available for DPN pain, which include acupuncture [60], near-infrared phototherapy [61], low-intensity laser therapy [62], transcutaneous electrical stimulation [63], frequency-modulated electromagnetic neural stimulation therapy [64], high-frequency external muscle stimulation [65], and as a last resort, the implantation of an electrical spinal cord stimulator [66].

The integrity of joints, muscles, and neural structures, especially the small joints and intrinsic muscles of the foot and ankle, is compromised as neuropathy progresses, resulting in poor dynamic stability of the foot, inadequate foot mobility, and impaired locomotor tasks. All of these losses have an impact on load absorption and transmission while the patient is walking, exposing the foot to mechanical overloads that lead to tissue breakdown and decreases the quality of life [67].

Most of the treatments that diabetic patients receive are passive. Plantar load relief is only recommended when critical neuropathy outcomes, such as foot deformities, ulcerations, and amputations, are already present. Active and preventive therapeutic actions, on the other hand, are strongly recommended for delaying or even preventing sensory, motor, and tissue complications, thus reducing the effect of disease on quality of life [68–70].

The uniform distribution of plantar pressure is hampered by foot deformities and defects in the extrinsic and intrinsic foot and ankle muscles. These factors cause the toes and hallux to participate inefficiently while the foot swings during walking, making the individuals at a higher risk of tissue damage. Ulceration is linked to both restricted joint mobility and high plantar loads. Thus preventive measures for the maintenance of joint mobility are highly recommended from the onset of disease [71, 72].

The reduction of tissue stress is considered as the main goal of interventions in patients with neuropathy. Those are achieved by prescribing shoes and custom-made insoles, orthotics with rocker soles. The primary aim of these orthotic devices is to change the foot rollover and thus passively redistribute plantar pressure. Exercise therapy for the foot and ankle, on the other hand, has the potential benefit of actively adjusting the foot loading, resulting in improvements in force absorption and transmission due to improved muscle function and joint stability. Thus, the use of an orthotic device for the prevention of foot ulceration along with a regimen of therapeutic exercises to improve the functionality of the individual's foot is recommended [73, 74].

Even though exercises do not directly prevent ulcer development, they do target musculoskeletal defects by trying to maintain or enhance the muscle and joint function of the distal segments, which can lead to improved individual functioning, a better health status, a higher quality of life, and a lower risk of falling [75–77]. Therapeutic exercises also enable patients to maintain for as long as possible the

residual biomechanical capability of interacting safely with the ground while walking and standing, and they can potentially be associated with prevention of tissue breakdown. Interventions that combined foot-ankle strengthening exercises and balance exercises showed improvement in the support time during single stance, tandem, and functional reach as well as in the equilibrium and confidence scores on their Activities Specific Balance Confidence Scale Questionnaires [78, 79]. Also gait training strategies to reduce plantar loads have shown modest results in neuropathic individuals. The proposed exercise program aims to integrate peripheral benefits for foot function during everyday locomotor activities using segmental exercises (muscle strengthening and range of motion). The clinical outcomes were favorable, with improvements in foot muscle control, foot and ankle function, and neuropathy symptoms. For further information on the therapy of painful polyneuropathy, refer to chapter on Peripheral Neuropathy Treatment and Management.

5. Conclusion

The screening of symptoms and signs of diabetic peripheral neuropathy is essential in all diabetic patients for an early recognition and management of diabetic neuropathies.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 7

Peripheral Neuropathy in ANCA Vasculitis

Mouna Snoussi, Faten Frikha and Zouhir Bahloul

Abstract

Antineutrophil cytoplasmic antibodies (ANCA)-associated diseases are necrotizing systemic vasculitides that affect small blood vessels (arterioles, capillaries and venules). This entity represents three main systemic vasculitides: granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss' syndrome). Their clinical manifestations are polymorphous, being the most frequent respiratory, oto-laryngo-pharyngeal and renal involvement. Peripheral neuropathy (PN) is reported in almost 50% of the patients. The aim of this chapter is to discuss the prevalence, clinical presentation, treatment and prognosis of PN in ANCA-associated vasculitis.

Keywords: ANCA vasculitis, peripheral neuropathy, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, eosinophilic granulomatous with polyangiitis

1. Introduction

Anti-neutrophil cytoplasmic antibodies-associated vasculitides (AAV) are rare autoimmune diseases of unknown etiology. They are characterized by cell inflammatory infiltration and necrosis of small vessels [1]. They are classified as microscopic polyangiitis (MPA) granulomatosis with polyangiitis (GPA, previously known as "Wegener's granulomatosis") and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as "Churg-Strauss syndrome") [2]. The systemic inflammation seen in these vasculitis result in organ- and life-threatening diseases with a polymorphous clinical presentation. AAV can affect the peripheral nervous system and that could be difficult to diagnose and treat. In cases of pre-existing systemic vasculitis, the diagnosis is easier to make, but when the vasculitis neuropathy is the initial or unique manifestation of the vasculitis, it requires careful clinical, neurophysiological, laboratory and sometimes histopathological investigation. The frequency of vasculitis-related neuropathy is variable and depends on the type of vasculitis [3]. In this chapter, we will discuss the pathogenesis, diagnosis, treatment and prognosis of neuropathies in AAV including the MPA, GPA and EGPA.

2. Pathogenesis of peripheral neuropathy in ANCA vasculitis

Peripheral neuropathy in AAV is caused by thrombosis and ischemic damage of the vasa nervorum. Different etiological agents may induce vascular

inflammation [4]. Vascular injury is associated with neoantigens (usually infectious) on the endothelium and neutrophils. Eosinophils contribute to vessel inflammation, as seen in GEPA [5]. Immune complexes with certain immunochemical characteristics activate a complement cascade that induces neutrophil-mediated damage to the vessel wall. The presence of granulocytes is associated with fibrinoid necrosis as they release toxic enzymes during inflammation. Antineutrophil cytoplasmic antibodies identify constituents of neutrophil cytoplasm including proteinase 3 (PR3), myeloperoxidase (MPO) and elastase. The release of these cytoplasmic components induces the release of inflammatory mediators such as TNFα [6]. Inflammation of vasa nervorum leads to ischemia with axonal degeneration that mainly presents as mononeuritis multiplex [7].

3. Epidemiology of peripheral neuropathy in ANCA-associated vasculitis

Peripheral neuropathy is common in ANCA-associated vasculitis and can be the first manifestation of the disease. The prevalence of PN is variable depending on the type of AAV. It is particularly higher in EGPA (60–80%) than in MPA (40–50%) and GPA (20–25%) [8–14]. Vasculitis-related neuropathies are also seen in other systemic diseases such as cryoglobulinemic vasculitis associated with chronic hepatitis C virus (HCV) with a prevalence of 60% and in primary Sjogren syndrome [14] and rarely in large-vessel vasculitis [14] and other connective tissue diseases such as systemic lupus [15].

4. Symptoms and clinical features of the neuropathy in ANCA-associated vasculitis

PN is usually the first clinical presentation of systemic vasculitis especially in EGPA and MPA. In other cases, the PN is associated with systemic symptoms of the disease such as asthenia, weight loss, fever, arthralgia or arthritis and vascular purpura. PN is characterized by an acute onset of pain, weakness and sensory loss that predominantly affects the distal portion of the extremity. Initially, the PN may present as a mononeuritis evolving over weeks or months later into multifocal neuropathy or mononeuritis multiplex [16]. The pain is described as throbbing and aching rather than burning. The lower limbs are usually affected and the most common involved nerve is the deep peroneal nerve [11–14, 17–22]. In the upper limb, the ulnar nerve is the most common affected nerve [17]. The mononeuritis multiplex pattern evolves into an asymmetrical or symmetrical polyneuropathy pattern, which can progress into a generalized sensorimotor neuropathy [17]. Muscle weakness and atrophy is also variable inially mild but subsequently prominent [23]. Uncommon presentations of PN in AAV are symmetrical polyneuropathy from onset and pure motorneuropathy [17, 24].

5. Diagnosis and clinical results of peripheral neuropathy in ANCA-associated vasculitis

The diagnosis of vasculitis neuropathy in AAV is usually easier in patients already presenting with multiorgan involvement and mononeuropathy multiplex. However, the diagnosis may be more cumbersome in less typical presentations of AAV or when peripheral neuropathy is the unique manifestation of the disease.

In these situations, the diagnosis is helped by focusing on the medical history, physical examination, electrodiagnostic study and nerve biopsy. Electrodiagnostic testing reveal an axonal neuropathy with reduced sensory and motor nerve action potential amplitudes [25–28] with better preservation of the nerve conduction velocities and distal latencies. These findings are more often in the lower limbs [28]. The nerve biopsy should be guided by the nerve conduction studies and include the nerve and neighboring muscle, such as sural nerve and neighboring gastrocnemius or superficial peroneal nerve biopsy and peroneus brevis muscles [17, 22, 29–31]. Muscle biopsy may increase the diagnostic sensitivity when concomitantly performed with the nerve biopsy [32]. Nerve biopsy results supportive of vasculitic neuropathy include the presence of vessel wall inflammation with vascular damage; vascular deposits of immunoglobulin M, C3, or fibrinogen, hemosiderin deposits on direct immunofluorescence, asymmetric nerve fiber loss, prominent active axonal degeneration, and myofiber necrosis, regeneration, or infarcts in the peroneus brevis muscle biopsy [23, 32].

6. Particularity of PN in ANCA-associated vasculitis

6.1 PN in eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis formerly named Churg–Strauss syndrome is a systemic small-vessel vasculitis associated with asthma and eosinophilia. It was first described in 1951 by Churg and Strauss [33] who remarked the association between asthma, eosinophilia, systemic symptoms and the presence of necrotizing and granulomatosis vasculitis in different organs especially in the peripheral nerves [33]. EGPA is a rare disease, with an annual incidence of 0.5–4.2 cases per million inhabitants [34]. It affects people aged between 40 and 60 years with no gender predominance or ethnic predisposition [35, 36]. In 1990, the American College of Rheumatology (ACR) defined the classification criteria for EGPA to include asthma, eosinophilia >10%, neuropathy, non-fixed lung infiltrates, paranasal sinus abnormalities and extravascular eosinophils on biopsy (**Table 1**) [37].

A histologic diagnosis was required in the Chapel Hill classification in 1994 and 2012 [2, 37, 38]. EGPA is a necrotizing vasculitis with an eosinophilic-rich, granulomatous inflammation affecting small- to medium-sized blood vessels in the respiratory tract.

EGPA should be suspected in a patient with an adult-onset asthma in association with multiple systemic symptoms and a subacute asymmetric neuropathy. Asthma of variable severity is noted in 95–100% of patients and could precede the systemic manifestations by many years. Allergic rhinitis, recurrent sinusitis and nasal polyposis are also seen in the prodromic EGPA phase [39–41]. Eosinophilic cell infiltrates are

1. Asthma
2. Eosinophilia >10%
3. Neuropathy (mono- or poly-neuropathy)
4. Non-fixed pulmonary infiltrates
5. Paranasal sinus abnormalities
6. Extravascular eosinophil infiltration on biopsy
At least four of the six ACR criteria are required.

Table 1.
ACR classification of EGPA [37].

found in the lung, heart and gastrointestinal tract. The lung parenchyma is affected in up to two-thirds of EGPA patients [41]. Chest X-ray abnormalities generally consist of mainly peripheral, patchy and migratory infiltrates. On high-resolution CT, they appear as ground-glass opacities or poorly defined areas of consolidation, which often coexist with abnormalities due to lower airway involvement, such as tree-in-bud signs, bronchial wall thickening and small centrilobular nodules [41]. The second type of lung involvement is alveolar hemorrhage, which affects 3–8% of the patients [13, 41]. Heart involvement is a poor prognostic factor of the disease and correlated with the level of eosinophilia. Endomyocardial infiltration is the dominant feature, but coronary vasculitis, pericarditis and valvular defects may also occur [42]. Venous thromboembolic events, such as deep venous thrombosis and/or pulmonary embolism, are associated with eosinophilia [43]. Renal involvement can also be seen ranging from isolated urinary abnormalities (i.e., microscopic hematuria, proteinuria) to rapidly progressive glomerulonephritis. Skin lesion such as purpura, nodules, urticaria, livedo, and skin ulcers could also be reported mainly in the lower limbs [41].

PN is considered a cardinal feature of the vasculitic phase with a prevalence of 70% [41, 44, 45]. PN is often associated with generalized signs and symptoms of fever, weight loss, and weakness. It usually presents as a mononeuritis multiplex, often complicated by asymmetric foot or wrist drop, but it may also evolve into a symmetric or asymmetric polyneuropathy [41]; sensory deficits and neuropathic pain are frequent [19, 26]. PN is more frequent in ANCA-positive patients than in patients without ANCA antibodies [41, 44].

Laboratory findings in EGPA include a marked peripheral eosinophilia (usually >1500 cells/μL), which correlates with disease activity [46]. C-reactive protein and erythrocyte sedimentation rate are also high in the active phase [41]. ANCA with perinuclear immunofluorescence is noted in 74–90% [41]. Histologic confirmation is the key diagnosis with leukocytoclastic vasculitis with eosinophilic granulomas in biopsy sites such as the lung or kidney. Granulomas are rarely found in peripheral nerves [41].

6.2 PN in granulomatosis with polyangiitis

GPA is a systemic ANCA-associated granulomatous vasculitis whose lesions primarily affect the respiratory tract and kidneys [47]. Its annual incidence is 5–10/million with a prevalence of 24–157 cases per million. It occurs in both sexes at 65–74 years of age [48, 49]. GPA can affect the central and peripheral nervous system. Centrally, it can be responsible for strokes, brain masses, seizures, and meningitis. Peripherally, in the systemic form of the disease, it can present with a sensorimotor neuropathy or as a mononeuritis multiplex. Nasosinus involvement is observed in 70–100% of patients and present with epistaxis, nasal ulcers, nasal septum perforation and deformation (**Figure 1**) [50, 51]. The lungs are the second most common affected organ in 50–90% of patients and present with lung nodules, cavitations, infiltrates, pleuritis, pleural effusions, or alveolar capillary hemorrhages. Renal involvement affects 40–100% of patients with hematuria, proteinuria and renal failure due to segmental necrotizing and pauci-immune glomerulonephritis. Skin manifestations include vascular purpura, ulcers and nodules. The systemic symptoms include myalgia, arthralgia, anorexia, weight loss, ocular scleritis, episcleritis, uveitis, retinal alterations, retinal, thrombosis, orbital masses granulomatosis, myopericarditis, intestinal perforation and mesenteric vasculitis [50]. To make the diagnosis of PN related to GPA, it is necessary to consider all the clinical manifestations suggestive of systemic vasculitis like C-ANCA (anti-PR3) determination and histological evidence of necrotizing vasculitis, necrotizing glomerulonephritis or granulomatous inflammation from a relevant organ biopsy. In 1990, the American College of Rheumatology established criteria to help the diagnosis of GPA (**Table 2**) [52].

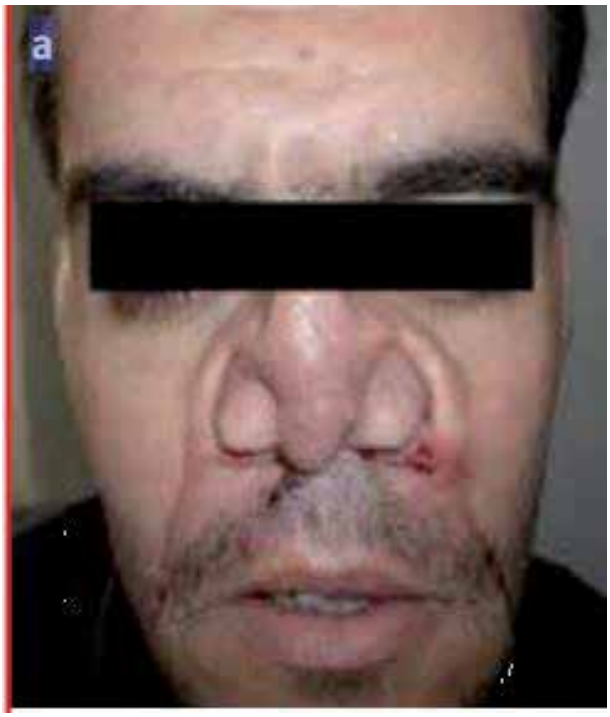

Figure 1.
Saddle nose deformity caused by bony destruction of the nasal cavity in a patient with Wegener's granulomatosis [50].

1. Sinus involvement
2. Alterations in pulmonary radiology
3. Alteration of urinary sediment (hematuria, hematic cylinders)
4. Histology revealing perivascular granulomas
At least two of the four ACR criteria are required to classify vasculitis as GPA with a sensitivity and specificity of 88% and 92%, respectively.

Table 2.
ACR classification of GPA [52].

6.3 Peripheral neuropathy in microscopic polyangiitis

Microscopic polyangiitis is an uncommon systemic vasculitis associated with perinuclear antineutrophil cytoplasmic (p-ANCA) or anti-myeloperoxidase (MPO). It was formerly considered as polyarteritis nodosa and in 1950, Wainwright and Davson used the phrase "microscopic polyarteritis" to describe this phenotype [53]. Microscopic polyangiitis predominates in men with an average age at onset between 50 and 60 years. Clinical manifestations include general symptoms of fever and weight loss in 70% of patients. Renal involvement is the main feature of MPA. It is characterized by a rapidly progressive glomerulonephritis in 80–100% of patients. It is shown by proteinuria in the nephrotic range in up to 50% of patients, microscopic hematuria, and urinary granular or red blood cell casts. Renal biopsy reveals focal segmental necrotizing glomerulonephritis in up to 100% of patients [54]. The second major organ being affected is the lung in 55% of patients. Clinical manifestations include hemoptysis and alveolar hemorrhage, infiltrates, pleural effusion, pulmonary edema, pleuritis and interstitial fibrosis. These symptoms are related to diffuse alveolar hemorrhage [55].

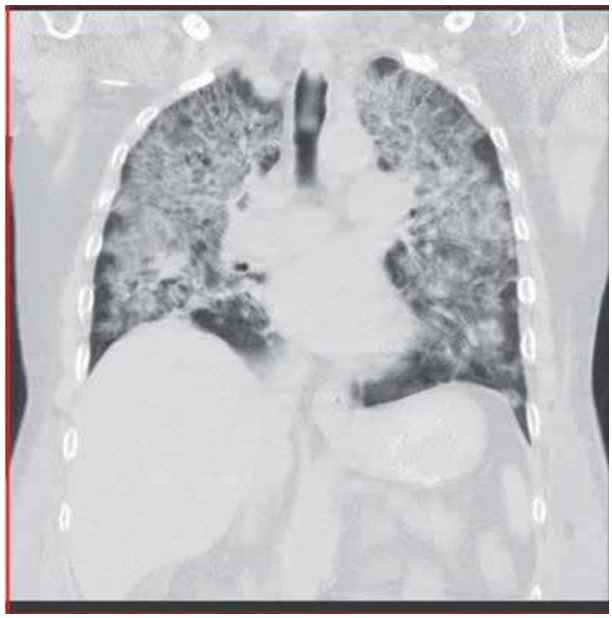

Figure 2.
Coronal chest CT scan image with diffuse bilateral ground glass infiltrates and focal areas of consolidation [55].

Computed tomography is necessary to confirm alveolar hemorrhage demonstrating the ground-glass attenuation (seen in >90% of patients) interstitial chronic inflammation of the alveolar septa and capillaritis (**Figure 2**) [55]. Skin lesions occur in 30–60% of patients being vascular purpura the main presentation. Other skin manifestations include livedo reticularis, nodules, urticaria and skin ulcers with necrosis. Skin manifestations are usually accompanied with arthralgia [54]. Neurologic involvement is common and affects between 37 and 72% of the patients. PN is a predominant feature that presents with a mononeuritis multiplex and distal symmetrical polyneuropathy [53]. Other clinical symptoms are gastrointestinal bleeding, intestinal ischemia, and liver dysfunction [54]. ANCA is the laboratory test that facilitate the diagnosis and is positive in 50–75% of patients with MPA, but its absence does not exclude its diagnosis. Biologic markers of inflammation are elevated such as erythrocyte sedimentation rate and C-reactive protein [56]. The diagnosis of the disease is based on clinical symptoms and biopsy of the affected organs.

7. Treatment of peripheral neuropathy in ANCA-associated vasculitis

The treatment is based on induction therapy and maintenance therapy. Unfortunately, there is not an universal protocol (dose or duration) for each form of therapy. Induction therapy is based in the combination of corticosteroids and cyclophosphamideor rituximab. Standard initial therapy consist of high-dose corticosteroids (prednisone 1 mg/kg/day) or IV methylprednisolone (1 g every day for three days and then once a week for three months) followed by a taper. Pulses of methylprednisolone are used in severe cases (i.e., mononeuritis multiplex and organ-threatening disease). Pulse IV cyclophosphamide (1 g/m^2 per month for six months; or 15 mg/kg every two weeks for three doses and then every three weeks for three to six months) is simultaneously started with corticosteroids, especially in more severe cases. Cyclophosphamide is adjusted by age (>60 years) and to renal function and leukocyte counts. IV Rituximab at 375 mg/m^2 per week for four weeks

Proteinuria >1 g/24 h
Creatinemia>140 μmol/L
Specific gastrointestinal involvement
Specific cardiomyopathy
Specific CNS involvement
One point for each of these five items when present.

Table 3.
Five-factor score in AAV.

every six months in combination with corticosteroids could be also used as induction therapy [57, 58]. Rituximab is often used in less severe cases with insufficient data in more severe neurological manifestations, however, some case studies are promising [7]. The five factor score (FFS) (**Table 3**) could be used to assess the prognosis and mortality of vasculitis in the next few years and then to guide when a more aggressive therapy is required, usually when FFS > 1 [59].

After the induction therapy, a maintenance therapy follows with oral immunosuppressants drugs such as azathioprine (1 mg/kg/day to 2 mg/kg/day), methotrexate (7.5 mg to 25 mg weekly), mycophenolate mofetil (1 g to 1.5 g, 2 times per day) or IV Rituximab pulsations every six months [7, 60]. Oral cyclophosphamide is not recommended because of the risk of serious complications [60, 61] such as hemorrhagic cystitis, alopecia, leukopenia, myelodysplasia, neoplasm, etc.

The symptomatic management of neuropathic pain consist of tricyclic antidepressants (i.e., amitriptyline, imipramine, nortriptyline, etc.), serotonin-norepinephrine reuptake inhibitors (i.e., duloxetine, venlafaxine) or antiepileptic drugs such as gabapentin and pregabalin, which are preferred because their better bioavailability [58]. Kinesitherapy should be included in the management of motor disability. PN in AAV requires regular medical visits due to the relapse risk.

8. Conclusion

PN is one of the possible neurologic manifestations encountered by physicians in AAV. Therefore, it is important to take a detailed medical history and examination and adequate investigations to assess for an underlying systemic vasculitis that may be associated with the neuropathy. Mononeuritis multiplex is the most common features of PN in the AAV. The electrodiagnostic studies and nerve biopsy may help in the diagnosis of the disease and PN. When the PN precedes the diagnosis of vasculitis, the medical history and biologic test, especially ANCA test, are vital for diagnosis, but its absence does not exclude the disease. PN in AAV carries a prognostic factor because of the potential risk for motor complications. Therefore, rapid treatment with corticosteroids and immunosuppressant agents is almost warranted in all patients, especially in severe cases. Continuous follow-up of PN in AAV is essential because of frequent relapses.

Conflict of interest

Authors disclose no conflict of interest.

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Chapter 8

Upper Extremity Entrapment Neuropathy

Anil Didem Aydin Kabakçi

Abstract

Entrapment neuropathy is a condition characterized by motor, sensory and autonomic deficits that occur as a result of compression of the peripheral nerve at certain points along its anatomical course for different reasons. Although each peripheral nerve has anatomical or compression-appropriate areas, this can occur at any point along the course of the nerve. Entrapment neuropathies usually occur in areas where the nerve passes through a channel consisting of bone and fibrous tissue. External and internal factors play a role in the etiology of entrapment neuropathies. Among the factors that cause neuropathy, anatomical variations, trauma, metabolic diseases, tumors, synovitis and vitamin B6 deficiency are the most common ones.

Keywords: Nerve entrapment, upper extremity, neuropathy, compression, Carpal tunnel syndrome, Cubital tunnel syndrome, Cervical rib syndrome, Thoracic outlet syndrome, Guyon syndrome, Pronator syndrome, Anterior interosseus sydrome, Posterior interosseus syndrome, Suprascapular nerve compression syndrome, Keralgia paresthetica, Spiral groove syndrome, Quadrilateral space syndrome, Musculocutaneous nerve compression syndrome

1. Introduction

Entrapment neuropathy, impingement syndrome or compression neuropathy are clinical conditions that develop due to compression of peripheral nerves in various narrow spaces or tunnels along their anatomical course due to different reasons such as trauma, anomaly, tumor, metabolic disease [1–5]. "Entrapment", "Compression" or similar terms are used to indicate that the onset of the problem is not caused by the nerves, but that it develops secondary to external mechanical effects [6]. While some neuropathies are common, some are rare [3].

In general, these neuropathies are thought to occur in actively working young/middle-aged individuals (between the ages of 25 and 40), especially in predisposing professions or having a history of certain medical conditions, and in individuals between the ages of 40 and 60 (due to hormonal factors) [3, 4]. In order to diagnose entrapment neuropathy, the patient's clinical history and examination are very important. However, it can sometimes be difficult to diagnose only by clinical history and examination. At this stage, it may be necessary to using imaging techniques. Electrophysiological studies (including electromyography and nerve conduction studies) are the gold standard in detecting the presence of lesions and determining the location of impingement neuropathies and nerve damage [7–9].

After the impingement, a series of symptoms such as pain, change or loss of sensation, motor dysfunction and muscle atrophy are usually observed. The severity of the problem is directly proportional to the duration of exposure to compression, its shape, severity and size [1, 10]. Pain and loss of strength are the most common symptoms of entrapment neuropathies. Medical conditions such as rheumatoid arthritis, diabetes, pregnancy, and acromegaly may cause entrapment neuropathy to present a more rapid and severe clinical picture [6].

In this study, the definitions of entrapment neuropathies observed in the upper limb, their impingement levels, causes and clinical conditions that may be seen due to impingement were reviewed.

2. Upper extremity entrapment neuropathy

Entrapment neuropathies can occur in both the upper and lower limbs [3]. Entrapment neuropathies of the upper limbs are quite common. Among these, the most common is Carpal tunnel syndrome, then Cubital tunnel syndrome and then ulnar neuropathies [11, 12]. Although anatomical distributions of symptoms differ, these neuropathies contain a similar pathophysiology and treatment [13]. The nerves that innervate the upper extremity originate from the brachial plexus. The brachial plexus begins to form in the posterior cervical triangle and from here extends to the axilla where peripheral nerves are formed that will innervate the upper extremity [14]. After the peripheral nerves responsible for upper extremity innervation leave the brachial plexus, they first lie in the arm region and then in the forearm region. As the nerves course from the arm area to the forearm, they pass through relatively stable structures such as tunnels at the level of the elbow joint. These tunnels are affected by swelling in various clinical conditions such as kidney failure, diabetes, thyroid disease, or a fracture in the area, and cause compression of the travelling nerve. This situation affects the microvascular blood flow, leading to focal ischemia of the nerve. These pathophysiological processes manifest as pain, paresis, loss of sensation and muscle weakness in the areas where the nerve is distributed in the patient [13].

2.1 Etiology

External and internal factors play a role in the etiology of entrapment neuropathies. Anatomical features of the path in which the peripheral nerve travels, the movement pattern of the region where the nerve is compressed, some systemic and local diseases (rheumatoid arthritis, myxedema, acromegaly, synovitis, tenosynovitis, etc.), trauma, space-occupying lesions, incorrectly applied splints, corsets, casts and crutches external are within the factors. However, diabetes mellitus, uremia, avitaminosis and alcoholism are internal factors [5, 15].

2.2 Pathophysiology

Nerve entrapment can be acute or chronic. Acute nerve compression is the development of acute and sensory-motor paralysis in the innervation area as a result of irritation with external pressure where the peripheral nerve is superficial [1]. Chronic compression occurs when the nerve passes through a fibro-osseous canal and is continuously subjected to microtrauma and distortion. According to the Seddon's classification, chronic nerve entrapment is divided into 3 subgroups as neuropraxia, axonotmesis and neurometsis. Neuropraxia is the mildest form characterized by myelin sheath injury or ischemia in which axon and connective tissue are preserved. Improvement occurs within weeks and months. Axonotmesis is

more severe than neuropraxia. There is injury to the axon itself. Although it takes a long time, nerve regeneration is possible. However, there is no complete recovery in patients. Neurometsis is the most severe of them and involves the complete disruption of the axon, which is unlikely to heal [1, 16, 17].

2.3 Clinical symptoms

In entrapment neuropathies, clinical symptoms range from sensory abnormalities to pain, paresthesia, and motor paralysis. Sensory problems and pain are common symptoms in the early stages. Motor dysfunctions may occur in later [6].

2.4 Brachial plexus and upper extremity innervation

The brachial plexus is formed by the ventral primary rami of C5, C6, C7 and C8, and nearly allof the ventral primary ramus from T1. The rami passes between the scalenus anterior muscle and the scalenus medius muscle and reach the posterior triangle of the neck. The rami from C7 and C8 are larger than those from C5 and T1. Before the main nerves of the upper limb are formed, a complex branch exchange occurs between the ventral branches C5-T1. Trunks, divisions and cords of brachial plexus are formed with complex branch exchange. The upper trunk is formed by C5 and C6. The middle trunk is the continuation of C7. The lower trunk is formed by C8 and T1. Trunks are divided into anterior and posterior branches after a short course. These are called anterior and posterior divisions. The anterior and posterior divisions of the trunks form cords by performing a number of combinations among themselves. The posterior divisions of the three trunks unite and form the posterior cord behind the axillary artery. The anterior divisions of the superior and medium trunks unite and form the lateral cord. The anterior division of the inferior trunk form the medial cord. The cords divide into terminal branches. Terminal branches of lateral cord are musculocutaneus nerve and lateral root of median nerve. Terminal branches of posterior cord are axillary nerve and radial nerve. Terminal branches of medial cord are ulnar nerve and medial root of median nerve (**Figure 1**) [16].

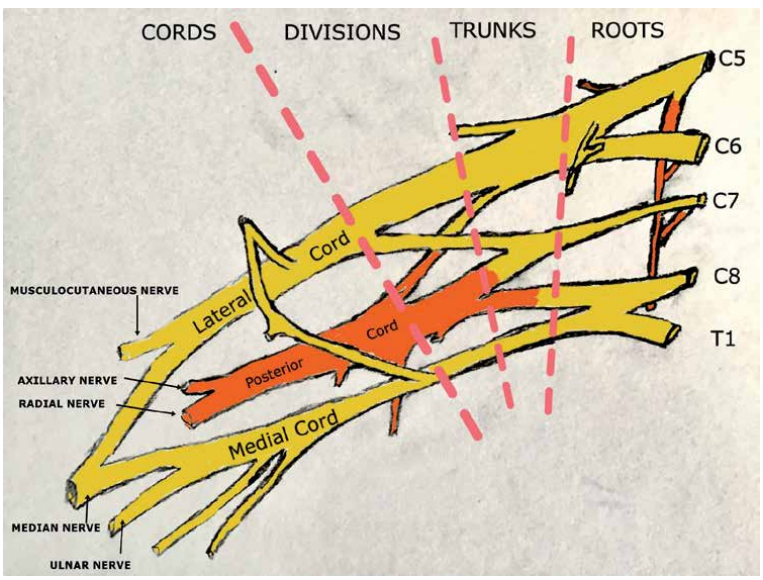

Figure 1.
Brachial plexus formation, roots, trunks, divisions and cords of the brachial plexus.

2.5 Basic entrapment neuropathies of the upper limbs

2.5.1 Compression neuropathies in the neck area

2.5.1.1 Cervical rib syndrome

Anatomy: The cervical rib is the accessory or extra rib originating from the 7th cervical vertebra. It can be found bilaterally or unilaterally and in varying sizes. The cervical rib is usually asymptomatic and is noticed incidentally on chest X-rays. Sometimes it can be palpated like a mass during the deep palpation of the supraclavicular region on physical examination. When it compresses the brachial plexus or subclavian vessels, it causes thoracic outlet syndrome or brachial plexopaty. This syndrome often causes pain in the hands when raising the arms (**Figure 2**) [18–20].

Description: It is a clinical congenital condition characterized by sensory and motor losses in the hand as a result of compression of the cervical rib or the C7 transverse extension to the C8 and T1 roots of the brachial plexus [18–20].

Causes: The accessory or extra rib originating from the 7th cervical vertebra.

Clinical features: Generally, there is a loss of sensation in the inner surface of the forearm and the last two fingers (ring and little fingers). Tingling and numbness could be in patients forearm and hand ulnar part. Pain in the upper extremity, atrophy of the intrinsic muscles of the hand, and vasomotor changes may occur. Cervical ribs may be associated with a weak pulse from the radial region, especially when the arm is abducted [20].

2.5.1.2 Thoracic outlet syndrome (TOS)

Anatomy: The thoracic outlet formed by the clavicle and the first rib is an anatomical region in the lower part of the neck through which important neurovascular structures. The thoracic outlet contains 3 spaces, called the interscalene triangle, costoclavicular space, and subcoracoid space, where neurovascular structures can

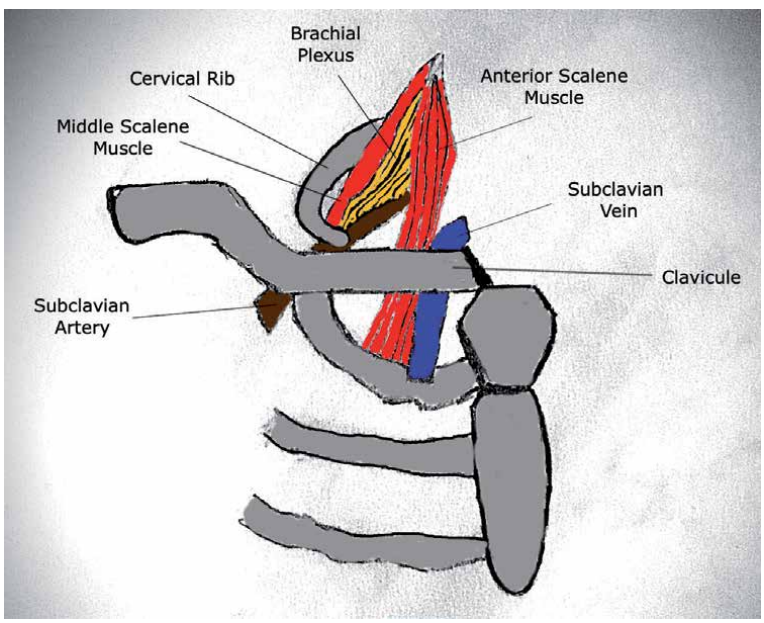

Figure 2.
The schematic drawing of close relationship between cervical rib and brachial plexus.

be compressed. The first anatomical stenosis encountered while the neurovascular bundle moves from the lower part of the neck towards the axillary region and the proximal part of the arm is an interscalene triangle. This triangle is bordered anteriorly by the anterior scalene muscle, posteriorly by the middle scalene muscle and inferiorly by the medial surface of the first rib. Brachial plexus and subclavian artery are located in this triangle. The 2nd and 3rd anatomical stenosis regions are the costoclavicular space, and the subcoracoid space. The middle third of the clavicle from the anterior, the first rib from the posteromedial and the upper order of the scapula from the posterolateral form the borders of costoclavicular triangle. The third space is the subcoracoid space under the coracoid process. The brachial plexus or its branches can be compressed in one of these spaces (**Figure 3**) [21, 22].

Description: Thoracic outlet sydrome is a condition that compression of the neurovascular bundle (brachial plexus and subclavian vessels) exiting the thoracic outlet [1, 21].

Causes: The compression that causes the syndrome can occur due to various anomalies of the bone and soft tissues. Bony abnormalities include the abnormal protrusion of the first rib or clavicle, the presence of a cervical rib, improper union or nonunion of the bone after fracture, or bone healing with excess callus

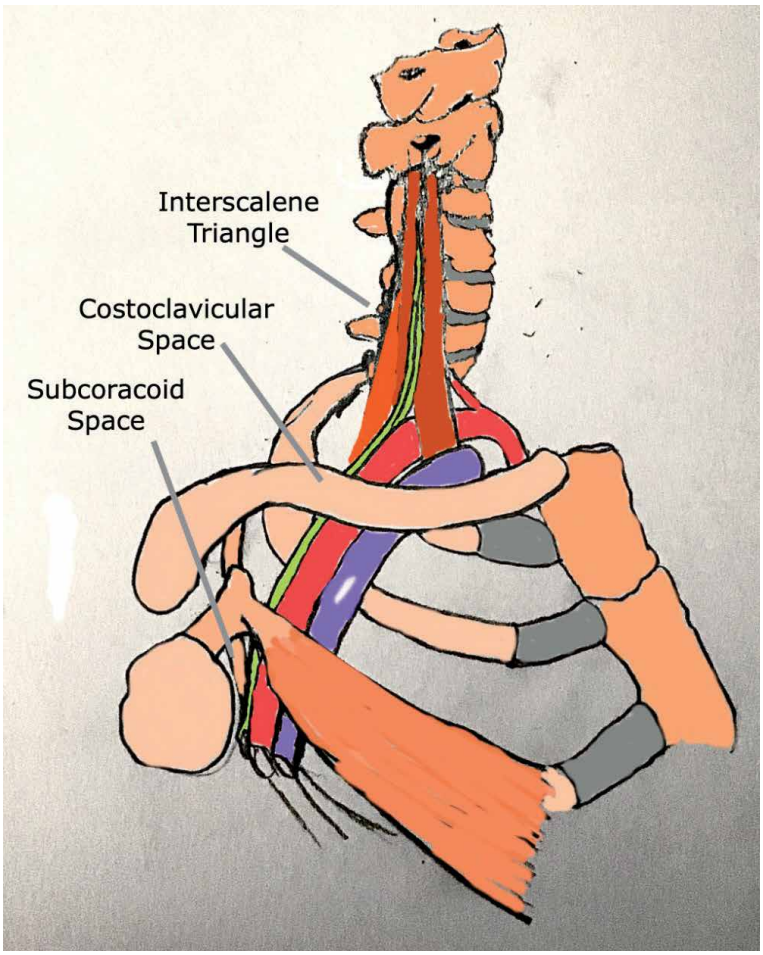

Figure 3.
The schematic drawing of entrapment sites (interscalene triangle, costoclavicular space, subcoracoid space) of the brachial plexus in the thoracic outlet syndrome.

tissue and retrosternal dislocation of the clavicle. Soft tissue anomalies include such as the presence of a fibrous band in the interscalene triangle, the presence of accessory neck muscles (minimus scalene muscle), anterior scalene hypertrophy, variations in scalene muscles and soft tissue tumors such as a Pancoast's tumor [1, 21]. It has been reported that congenital or post-traumatic malformations can cause compression, as well as due to occupational disease or due to excessive use in athletes who frequently perform overhead and throwing activities [23, 24]. Repeated overhead use by athletes engaged in this sport leads to loss of stability of the shoulder girdle and hypertrophy of the scalene muscles and pectoralis minor muscle. As a result, compression may occur in neurovascular structures in the region [25].

Clinical features: Neurogenic TOS involve include paresthesia, numbness,, and weakness radiating from the neck region and shoulder and extending into the arm and hand. TOS can cause paresthesia in a wide area. Symptoms can be seen unilateral or bilateral. Pain is felt especially over the trapezius muscle [1, 9, 24].

2.5.2 Impingement syndromes around the shoulder

2.5.2.1 Suprascapular nerve compression syndrome

Anatomy: The suprascapular nerve is a peripheral nerve with motor and sensory fibers that originates from the C5-C6 nerve roots and leaves the upper trunk of the brachial plexus. After passing through the posterior cervical triangle, it runs laterally, deep to trapezius and omohyoid, and enters the supraspinous fossa through the suprascapular notch, which is a fibro-osseous tunnel bridged by the transverse scapular ligament. The suprascapular nerve gives off two branches in the suprascapular fossa. One of these branches is distributed to the supraspinatus muscle, the other to the upper aspect of the shoulder joint. The nerve passes through the lateral part of the scapular spine and reaches the spino-glenoid notch. It reaches the infraspinatus fossa by passing through this notch. It supplies the infraspinatus muscle and posterior aspect of the glenohumeral joint (**Figure 4**) [8, 16, 26].

Description: This clinical condition is characterized by the suprascapular nerve compression at the suprascapular notch or at the spino-glenoid notch [26].

Causes: Different pathologies play a role in the compression of the suprascapular nerve at the suprascapular notch and/or spino-glenoid notch. The reasons causing compression are grouped in 2 subgroups, primary and secondary. Primary reason is dynamic entrapment of the nerve. Causes such as space occupying lesions (neoplasm, ganglion cyst, ossified scapular ligament), traumatic conditions (scapula fractures, shoulder dislocation, massive cuff tear, distractive trauma, penetrating trauma), post traumatic disorders (hematomas, heterotopic ossification, hypertiroidisim) and systematic disorder are classified as secondary. In addition, hormonal alterations or iatrogenic conditions (arthroscopic tear cuff repair, Latarjet procedure) can also cause suprascapular neuropathy [8, 26, 27]. If suprascapular nerve entrapment occurs around the suprascapular notch, both supraspinatus and infraspinatus muscles; if the spino-glenoid occurs around the notch, only the infraspinatus muscle is affected [8]. Shoulder pain associated with suprascapular neuropathy is seen as secondary to trauma in people involved in sports, and repetitive stretching of the nerve, especially in overhead volleyball players, baseball players, basketball players and dancers, is shown as an etiological factor [26].

Clinical features: When the suprascapular nerve is entrapped at the suprascapular notch, both supraspinatus and infraspinatus muscles may undergo denervation. When the nerve is compressed at the spino-glenoid notch, denervation is limited to the infraspinatus muscle [8, 26]. Suprascapular neuropathy presents with

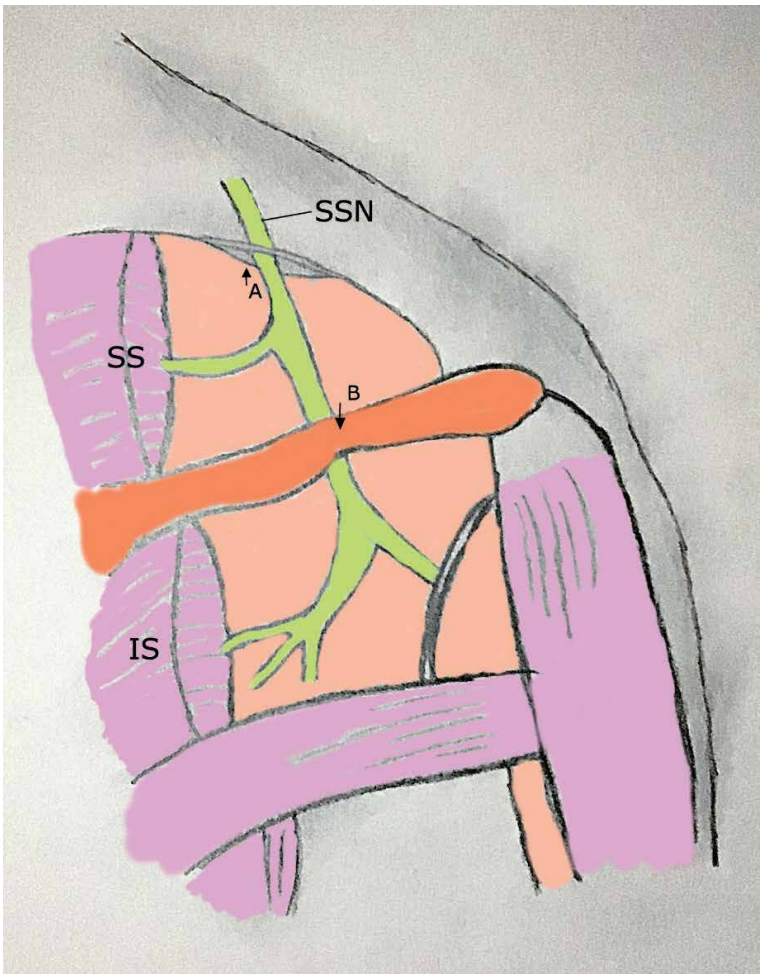

Figure 4.
The schematic drawing of entrapment sites in suprascapular nerve compression syndrome (entrapment sites are shown with a black arrow. A: The suprascapular notch, B: The spino-glenoid notch. SSN: Suprascapular nerve, SS: Supraspinatus muscle, IS: Infraspinatus muscle).

dull and poorly localized pain, often localized lateral and posterior to the shoulder. Patients have difficulty in raising the arm. Particularly the shoulder external rotation and abduction is weakened on the affected side and is often confused with cervical disc pathologies. If the impingement is in the suprascapular notch, the pain is more pronounced and the clinical noisier. Pain can spread to the neck and anterior rib cage wall. In addition, the suprascapular nerve is a purely motor nerve. So, no sensory loss is observed [8, 26–28].

2.5.2.2 Axillary nerve compression neuropathy (Quadrilateral space syndrome-QSS)

Anatomy: The quadrilateral space (QS) (**Figure 5**) is a space in the posterior aspect of the shoulder and bordered medially by the the long head of the triceps, laterally by the medial edge of the surgical neck of the humerus and inferiorly by the teres major and latissimus dorsi muscles and superiorly by the the teres minor muscle or the glenohumeral capsule. The QS contains the posterior circumflex humeral artery and the axillary nerve. Axillary nerve originates from the posterior

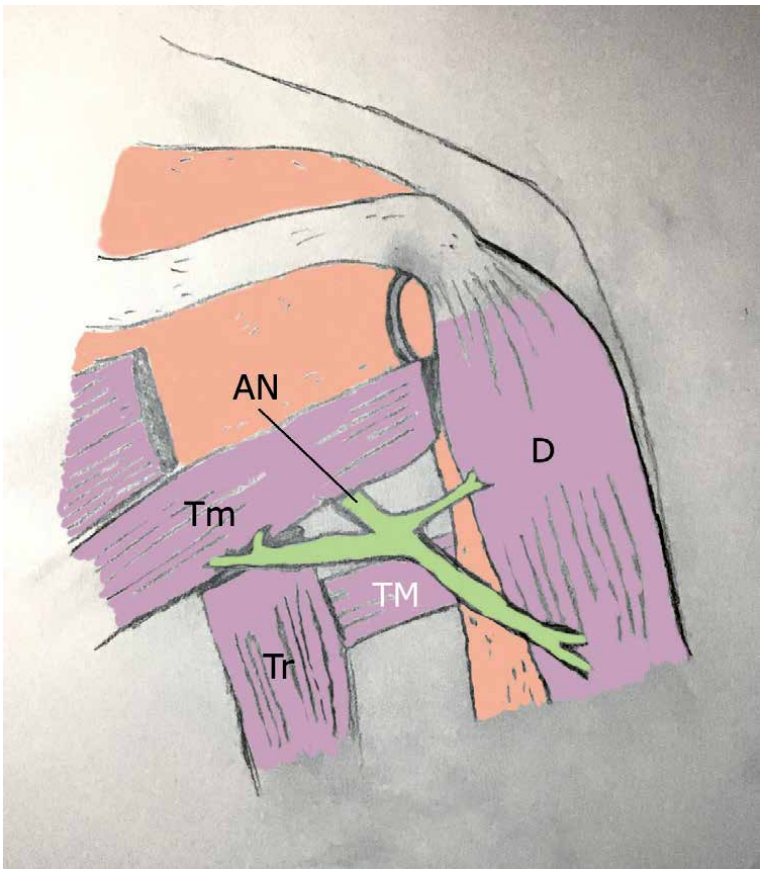

Figure 5.
The schematic drawing of entrapment site (quadrilateral space) in axillary nerve compression neuropathy AN: Axillary nerve, Tm: Teres minor muscle, Tr: Long head of the triceps, TM: Teres major muscle, H: Humerus, D: Deltoid muscle).

cord of the brachial plexus (C5-C6). It then runs along the inferolateral edge of the subscapular muscle and curves downward from the glenohumeral joint capsule to reach the OS. It divides into anterior and posterior branches in the space. The anterior branch curves together with the posterior circumflex artery around the humeral neck and reaches the deltoid muscle. At the acromion level, the nerve gives branches to supply the anterior deltoid and cutaneous branches that spread over the skin covering the deltoid muscle. The posterior branch innervates the teres minor and the posterior deltoid muscle and gives off branches to the skin over the distal part of the deltoid and the upper part of the long head of triceps [8, 16, 26, 29, 30].

Description: Quadrilateral space syndrome or axillar nerve compression neuropathy is a condition characterized by compression of the posterior humeral circumflex artery and axillary nerve in the quadrilateral space while the shoulder is in abduction and external rotation [29, 30].

Causes: Fractures of the upper limb, improper use of crutches, casts, fibrous bands, or inferior (from 9 to 7 o'clock positions) paraglenoid cysts may cause stretching injuries or stenosis of the quadrilateral space and OS contents may be compressed in QS. As a result, axillary neuropathy develops due to compression. Fibrous bands are the most common cause of compression in the QS. Also, space-occupying lesions in the QS (paralabral cyts, bony fracture fragments, being tumors), venous dilation and muscle hypertrophy have been implicated cause of cases of QSS [8, 26, 29, 30].

Clinical features: The patient has poorly localized lateral and posterior shoulder pain and weakness, which is exacerbated by abduction and external rotation of the arm. Generally, pain becomes evident at night, after overhead activities and in the late phase of throwing. In a non dermatomal distribution, paresthesias of the affected arm may be seen. Minimal axillary nerve sensory defect can be detected [8, 26, 30, 31]. QSS is difficult to diagnose because it shows similar characteristics to the symptoms of rotator cuff pathology or other shoulder joint-related abnormalities [8].

2.5.3 Impingement syndromes in the arm and forearm

2.5.3.1 Supracondylar process syndrome

Anatomy: The supracondylar process is a beak-shaped bone spur located on the anteromedial face of the distal part of the humerus. This congenital variation does not cause any symptoms in many people. It is located approximately 4 to 8 cm above

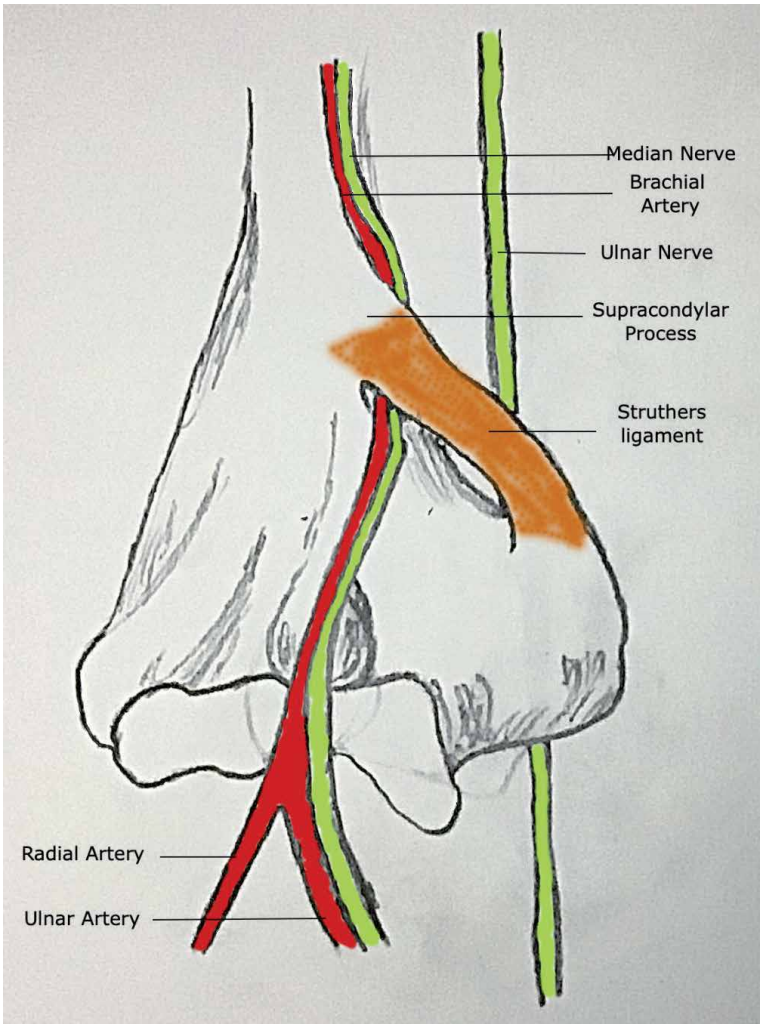

Figure 6.
The schematic drawing of median nerve between the Struther's ligament and the bony prominence (supracondylar process) in the distal humerus.

the medial epicondyle. The Struther's ligament, a fibrous band, is stretched between the tip of this bone spur and the medial epicondyle. The Struther's ligament, a fibrous band, is stretched between the tip of this bone spur and the medial epicondyle. The neurovascular structures that are most compressed in this entrapment site are the median nerve and the brachial artery (**Figure 6**) [32, 33].

Description: It is a condition characterized by the compression of the median nerve between the Struther's ligament and the bony prominence in the distal humerus [32–34].

Causes: Congenital bone spur in beak-shaped form located in the distal part of the humerus called the supracondylar process [32, 33].

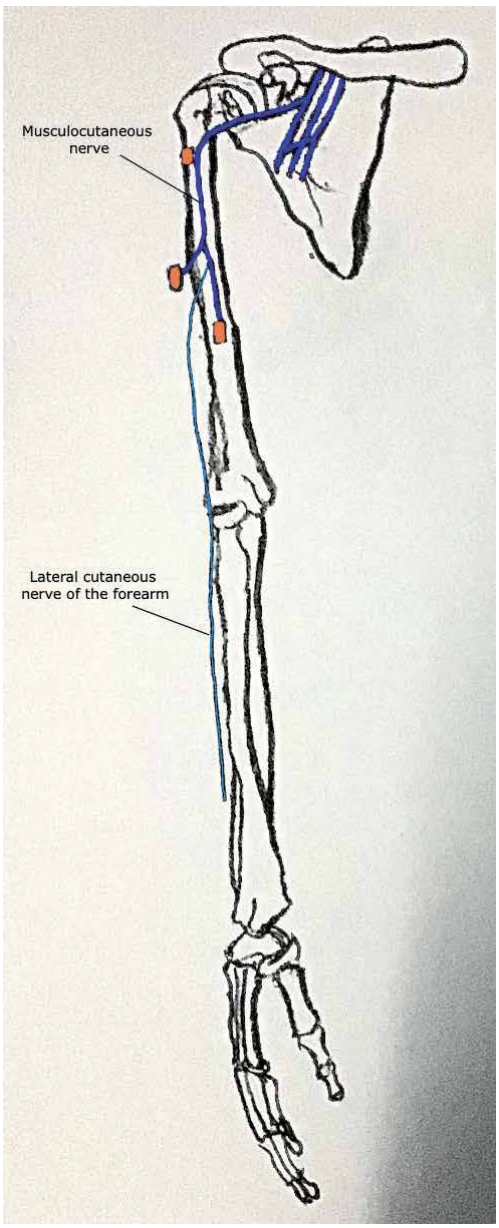

Figure 7.
The schematic drawing ofmusculocutaneous nerve and lateral cutaneous nerve of the forearm.

Clinical features: Symptoms are vascular and neuronal. Vascular compression symptoms are related to the brachial artery. Ischemic pain, forearm claudication and cyanosis may be seen. Pain, muscle wasting and numbness of the affected hand are symptoms that can be seen in nerve compression. Heavy manual work, repetitive activities and during flexion and pronation of the forearm may cause an increase in symptoms [34]. Prolonged median nerve compression may cause weakness and atrophy in some patients. Paresthesia and numbness may be seen at extension of the elbow [35].

2.5.3.2 Musculocutaneous nerve compression neuropathy

Anatomy: The musculocutaneous nerve originates from the lateral cord of the brachial plexus (C5–7), opposite the lower border of pectoralis minor. As the name suggests, it is a complex nerve. It innervates the biceps, coracobrachialis and brachialis muscles. It superficializes near the lateral edge of the bicipital aponeurosis and continues in the distal part of the forearm under the name of lateral antebrachial cutaneous nerve. It receives the sensation of the lateral part of the forearm [16, 36–42]. It contains only motor fibers above the elbow and only sensory fibers below the elbow (**Figure 7**) [16, 42].

Description: It is characterized by compression of the musculocutaneous nerve while travelling within the coracobrachialis muscle or at the point-where the lateral antebrachial cutaneous branch separating from the nerve is superficialized [9, 17, 38].

Causes: Musculocutaneous nerve entrapment is less common than others. Impingement usually occurs after trauma. Factors such as weightlifting, ball sport (throwing etc.), football, sleep, rowing, remote control sports (such as model airplane flying), prolonged repetitive forceful contracture of the elbow flexors such as following prolonged windsurfing, playing recreational basketball, humeral fractures, osteochondroma of the humerus, shoulder surgery, anterior shoulder subluxation, vigorous upper extremity exercise, coracoid process transfer are recommended foretiology of musculocutaneous nerve compression [7, 9, 36, 37, 39–41].

Clinical features: Compression of the musculocutaneous nerve causes wasting and weakness in the muscles innervated by the nerve. Patients may have dysesthesia on the lateral aspect of the forearm. Lateral cutaneous nerve (LACN) may be injured in situations such as venipuncture, cut-down procedure, compression. LACN is a purely sensory nerve. However, patients affected by LACN complain of pain rather than paresthesia. Symptoms caused by compression of the LACN may mimic other syndromes that cause elbow pain, such as lateral epicondylitis and radial tunnel [9, 36, 41].

2.5.3.3 Proximal radial nerve compression neuropathy (Spiral groove syndrome)

Anatomy: The radial nerve originates from the posterior cord of the brachial plexus and innervates the muscles of the extensor compartments of the upper extremity. After passing the axilla, the radial nerve windsclosely around the posterolateral aspect of the humeral shaft and descends along the spiral groove between the heads of the triceps muscle. The radial nerve innervates brachioradialis, extensor carpi radialis, and supinator muscles and skin overlying the posterior upper arm (posterior cutaneous nerve of the arm and lower lateral cutaneous nerve of the arm) [1, 7–9, 16, 26, 36]. Then, the radial nerve reaches the anterior compartment of the arm by piercing the septum approximately 10 to 12 cm above the lateral epicondyle and gives off superficial and deep branches [7].

Description: It is a condition characterized by compression of the radial nerve as it passes between the heads of the triceps muscle in the spiral groove (**Figure 8**) or a fibrous arch of the lateral head of the triceps muscle [7, 9].

Causes: During the course of the nerve in the spiral groove, its close relationship with the humerus and Intermuscular septum leaves the nerve vulnerable to impacts from outside. Humerus fractures, external compression (arm rest on the edge of the chair during unconsciousness from anesthesia, drugs abuse (alcohol), or during profound sleep-Saturday night syndrome, crutches use), long tourniquet application, professions that require repeated use of the triceps muscle, deep intramuscular injections of the arm are common causes of nerve compression [9, 26]. The most common cause of radial nerve compression in the axilla is improper use of crutches. Radial nerve compression neuropathy in the spiral groove. It is often referred to as "Saturday night paralysis". The reason for this name is the radial nerve compression caused by long-term unconsciousness of alcoholics [7–9, 35, 42].

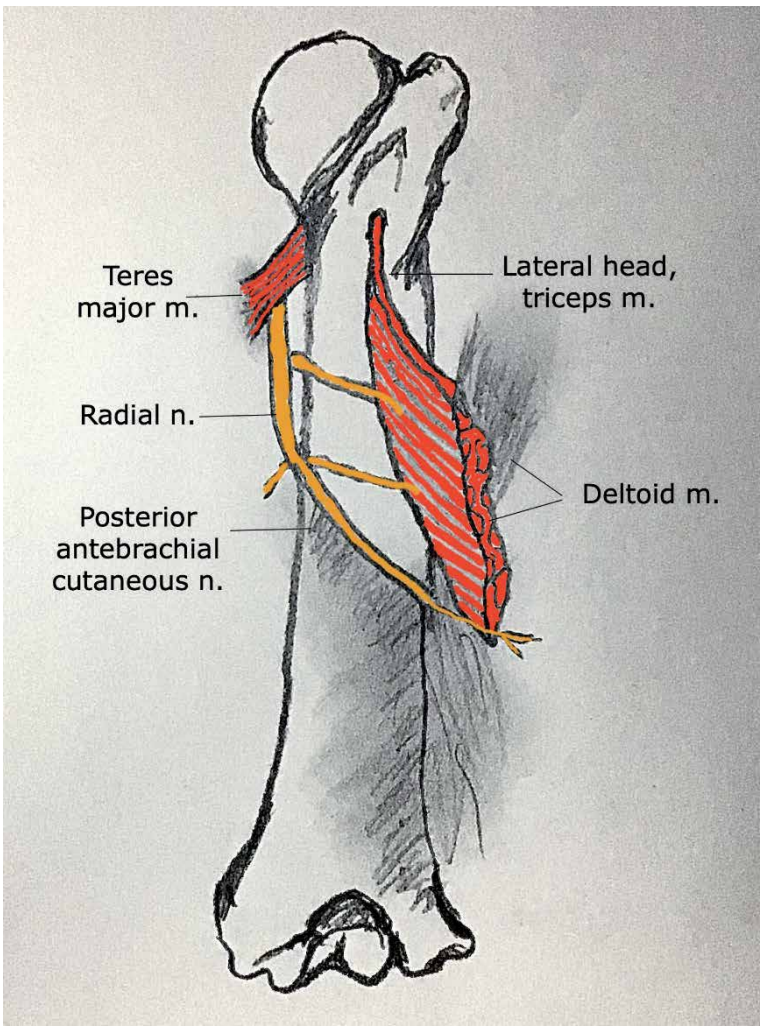

Figure 8.
The schematic drawing of the course of the proximal radial nerve in the spiral groove (n.:nerve, m.:musculus).

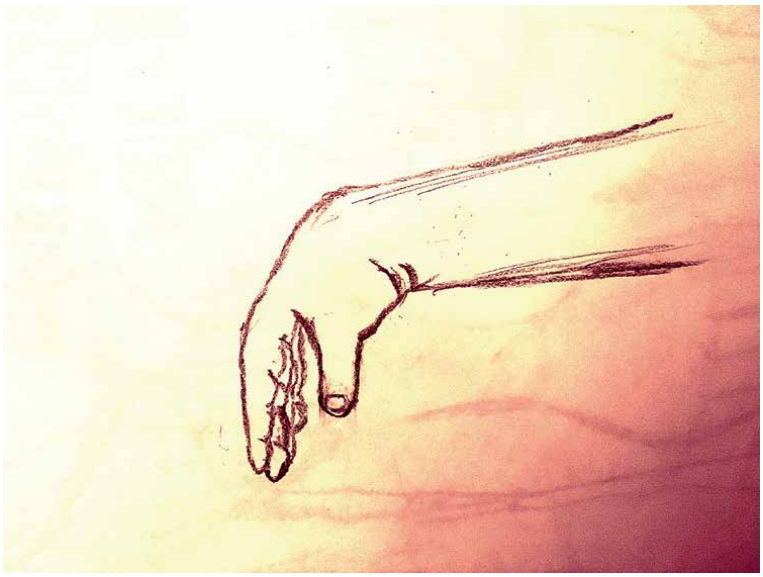

Figure 9.
"Wrist drop deformity" caused by compression of the radial nerve.

Clinical features: Loss of sensation and pain occur at the sensory dermatome of radial nerve where lateral of the elbow, the dorsal of the forearm and the dorsoradial of the hand in the slight compression of the radial nerve. The pain is further exacerbated by elbow extension, forearm flexion, and wrist flexion in the position where traction is exerted on the nerve. Pain that increases with resistant extension of the middle finger is an important finding of radial nerve entrapment neuropathy. As the pressure on the nerve gets longer, motor losses begin to occur. At this level, the triceps muscle is intact, there is paralysis in the supinator and brachioradialis muscles; However, since the biceps muscle with musculocutaneous nerve innervation is active, elbow flexion and supination movement are not restricted. There is paralysis in wrist extensors, finger extensors, thumb abductor and extensor. Therefore, this condition resulting from proximal radial nerve compression syndrome is called "Wrist drop deformity" (**Figure 9**) [7, 9, 26, 42, 43].

2.5.4 Impingement syndromes in the elbow

2.5.4.1 Cubital tunnel syndrome (ulnar neuropathy)

Anatomy: The ulnar nerve originates from roots C8 to T1 via the medial cord of the brachial plexus. It runs along the posterior aspect of the humerus on the arm, and the medial epicondyle pierces the intermuscular septum approximately 8 cm above it. It enters the posterior compartment of the forearm. The nerve passes under the arcade of Struther's in the presence of the Struther's ligament. At the level of the elbow, the ulnar nerve passes through a fibro-oesseus channel called the cubital tunnel that is bordered by the olecranon, medial epicondyle and Osborne ligament. A fascial structure between the olecranon and the medial epicondyle known as the cubital tunnel retinaculum (CTR) formed the roof of the cubital tunnel (**Figure 10**). The nerve then passes under the arcuate ligament formed by aponeurosis of flexor carpi ulnaris muscle and reaches the forearm. The ulnar nerve reaches the elbow joint level without giving any motor or sensory branches.

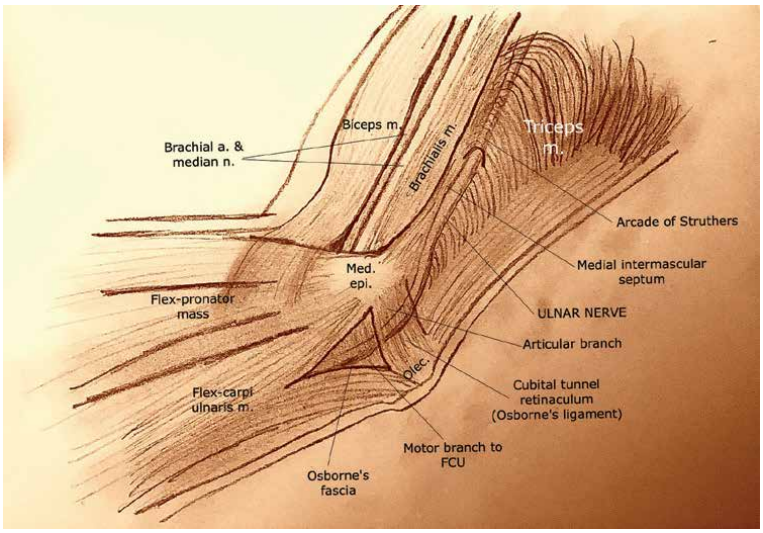

Figure 10.
The schematic drawing of cubital tunnel (a:Artery, n:Nerve, m:Muscle, med.Epi: Medial epicondyle, flex:Flexor, FCU: Flexor carpi ulnaris, Olec:Olecranon).

When it passes between the two heads of the flexor carpi ulnaris muscle, it gives motor branches to the flexor carpi ulnaris muscle [1, 7, 8, 9, 16].

Description: Cubital tunnel syndrome is the second most common impingement syndrome after carpal tunnel syndrome [26]. Due to its anatomical features, the ulnar nerve is most frequently compressed in the elbow area, where it is most susceptible to local compression and trauma. Posner [44] defined the 5 potential compression area in the elbow. These are the arcade of Struthers, the medial intermuscular septum, the cubital tunnel, retroepicondylar groove, and the flexor pronator aponeurosis. Although the term cubital tunnel syndrome refers to a specific anatomic point, compression neuropathy may be also outside the cubital tunnel. Cubital tunnel syndrome is a condition characterized by the compression of the ulnar nerve in the region of the elbow joint [45].

Causes: There are many reasons that can cause the development of ulnar neuropathy. Compression of the nerve in condylar groove, cubitus valgus, elbow fractures, osteoarthritis with medial osteophytes, and space occupying soft-tissue lesions, ganglia, and accessory muscles (eg, anconeus epitrochlearis muscle) are the most important known reasons [8, 9, 26, 45].

Clinical features: The complaint is generally in the form of pain radiating to the medial of the forearm, sensory abnormalities in the dorsal and palmar aspects of the hand, and motor weakness in the intrinsic muscles of the hand. In advanced stages, claw hand deformity(hyperextension of the metacarpophalangeal joints of the 4th and 5th fingers, flexion of the proximal and distal interphalangeal joints by the effect of extrinsic flexors) may occur. The little finger may also remain in a slightly abducted position (Wartenberg's sign) [8, 9, 26, 42].

2.5.5 Impingement syndromes in the forearm

2.5.5.1 Anterior interosseous (AIN) syndrome (Kiloh-Nevin syndrome)

Anatomy: The anterior interosseous nerve (AIN) originates from the median nerve. It is the terminal motor branch of the median nerve (**Figure 11**). After separating from the median nerve in the anterior part of the cubital fossa, it extends

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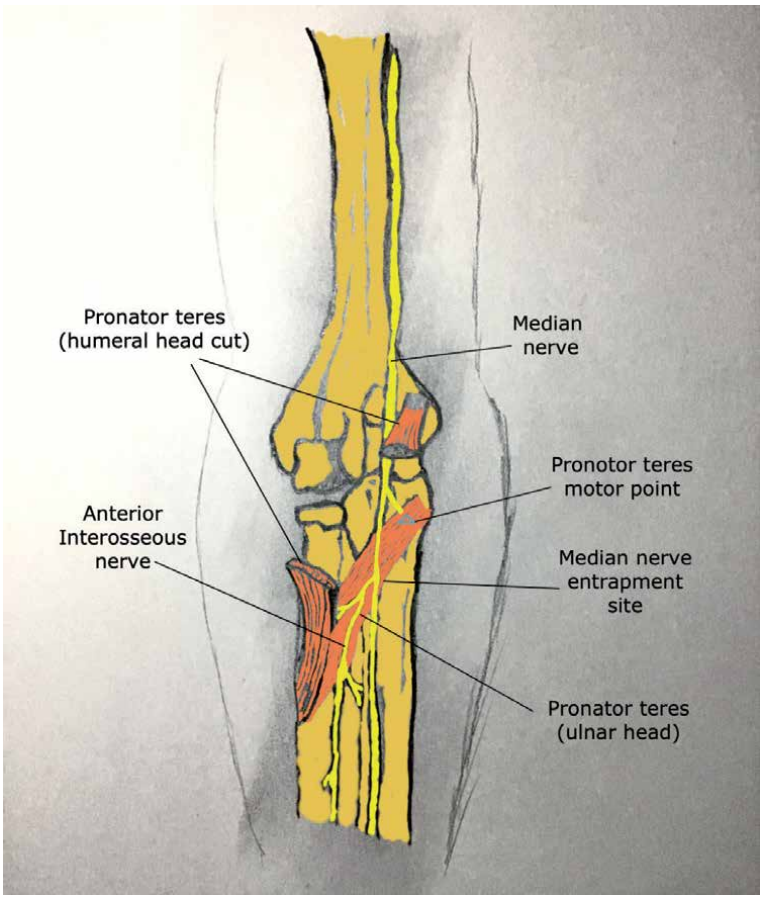

Figure 11.
The schematic drawing of anterior interosseus nerve between the pronator teres muscle heads.

on the forearm towards the wrist with the interosseous branch of the ulnar artery that accompanies it on the anterior face of the antebrachial membran. It courses between the muscle bellies of the flexor pollicis longus and flexor digitorum profundus at the forearm. The nerve innervates the flexor pollicis longus, radial part of the flexor digitorum profundus, the pronator quadratus muscles and middle and index fingers [1, 16, 24, 46–48].

Description: It is a condition characterized by compression of the anterior interosseous branch of the median nerve the proximal forearm [8].

Causes: There are many factors that may cause anterior interosseous nerve syndrome to occur. Causes may be spontaneous or traumatic. Supracondylar fractures, penetrating injuries, cast fixation, puncture of vein, internal fixation for fractures are considered within traumatic causes. Presence of supracondylar bony, compression of the nerve during the passage between two heads of pronator teres muscle, brachial plexus neuritis and hematoma and mass-induced nerve compression are spontaneous causative factors. The tendinous margin of the deep head of the pronator teres muscle is the most common site of AIN entrapment [8, 26, 46, 48].

Clinical features: The most obvious symptoms of AIN are pain and muscle weakness in the volar forearm, particularly at night, and difficulty in handwriting and pinching movements with the fingers. Symptoms may be increased by supination and extension. Motor dysfunction can be seen in AIN. Especially, patients complain that weakness in their thumb and index finger. Patients cannot make the

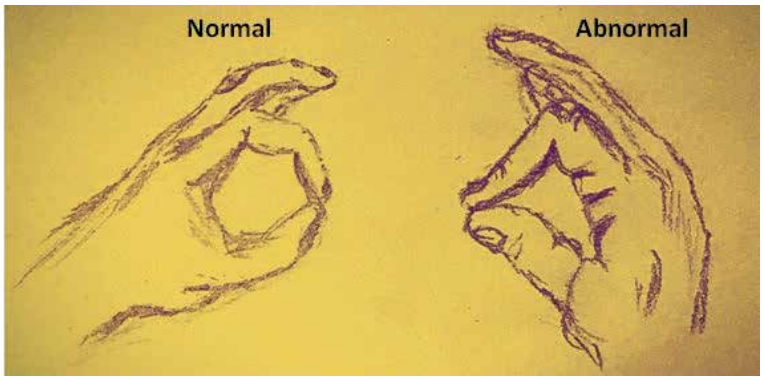

Figure 12.
Hand posture in anterior interosseous syndrome.

"OK" sign (**Figure 12**). Due to the Martin-Gruber anastomosis, paralysis may also occur in the intrinsic muscles of the hand [1, 8, 9, 26, 46, 48].

2.5.5.2 Pronator teres syndrome

Anatomy: The median nerve originates from the medial (C8 and T1) and lateral cords (C5 through C7) of the brachial plexus. At the elbow level, from medial to lateral, are the median nerve, brachial artery and the biceps tendon. The median nerve courses anterior to the brachialis muscle and deep to the Lacertus fibrosus. The nerve then courses between the superficial (humeral) and deep (ulnar) heads of the pronator teres muscle in the proximal third of the forearm and exits the cubital fossa (**Figure 13**) [16, 26, 49].

Description: It is a condition characterized by compression of the median nerve between the two heads of the pronator teres muscle or the pressure of the fibrous bands [8].

Causes: The nerve may be compressed due to thickened bicipital aponeurosis, Struther's ligament, the arch of the flexor digitorum superficialis,as well as the hypertrophic pronator teres muscle, aberrant median artery, crossing branch of the radial artery, or soft tissue mass [8, 9, 49].

Clinical features: With resistant wrist flexion and forearm pronation, symptoms increase. The pain is localized to the medial of the forearm. Paresthesia and sensory problems are seen in the first three fingers of the hand, which is the dermatome area of the median nerve. In addition, weakness may occur in the intrinsic and extrinsic muscles of the hand innervated by the median nerve [8, 9, 49].

2.5.5.3 Posterior interosseous nerve (PIN) syndrome (Supinator syndrome)

Anatomy: The radial nerve originates from the posterior cord of the brachial plexus and innervates the muscles of the extensor compartments of the upper extremity. After the course of the radial nerve in the arm, the nerve reaches the anterior compartment of the arm by piercing the septum approximately 10 to 12 cm above the lateral epicondyle and gives off superficial and deep branches (**Figure 14**) [1, 4, 7]. The deep branch (posterior interosseus nerve-PIN) of the radial nerve first wraps around the radial neck and then travels within the radial tunnel. The radial tunnel is bordered medially by brachialis and biceps tendon and laterally by extensor carpi radialis longus and brevis. The PIN then passes below the superficial layer of supinator (which is known as the arcade of Frohse) and innervates supinator as

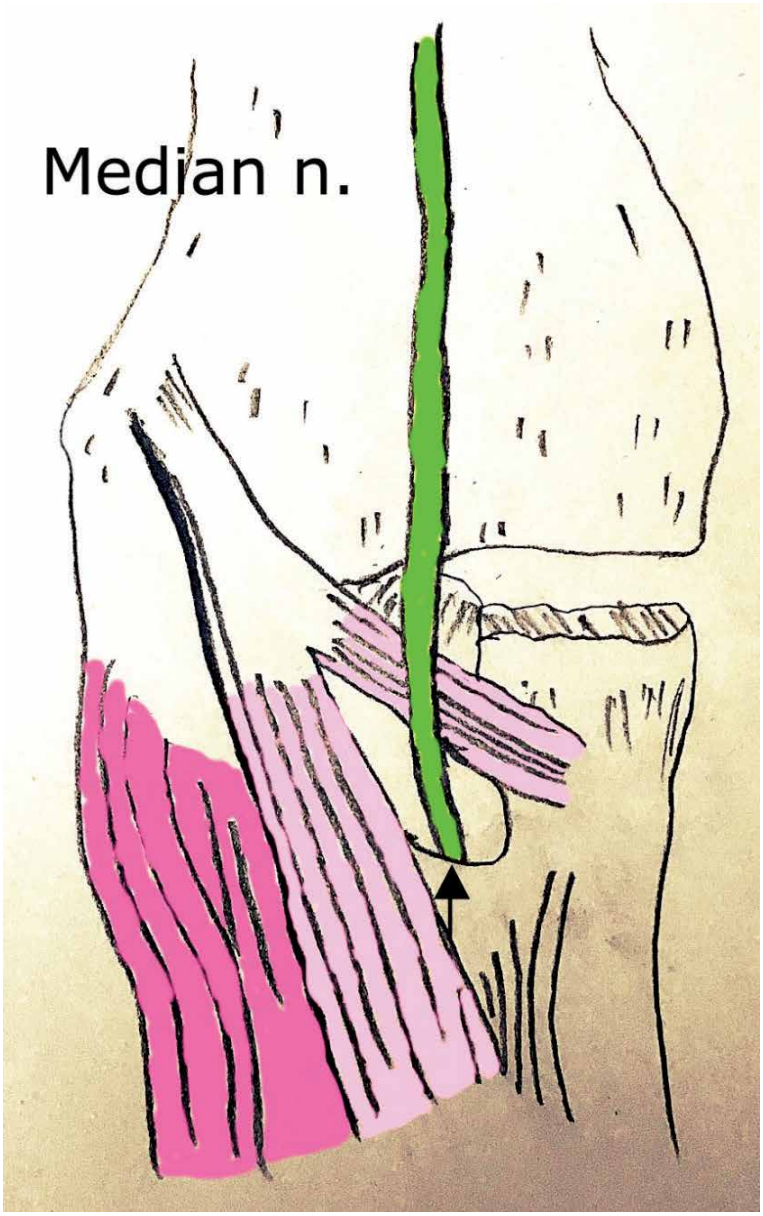

Figure 13.
The schematic drawing of median nerve between the pronator teres muscle heads.

well as wrist and finger extensors. The superficial branch of the radial nerve runs along the radial artery in the forearm. It passes over the first extensor compartment at the wrist and disperses on the back of the hand [1, 8].

Description: Posterior interosseous nerve syndrome is a condition characterized by compression of the nerve in the proximal forearm, anterior to the elbow capsule, under the Frohse archade, approaching the arch, or within the supinator muscle [1, 8, 9].

Causes: In some professions such as athletes and violinists, excessive use of the arm, use of crutches, repetitive pronation-supination movement, fractures of the radial head, soft tissue tumors such as ganglion and lipoma, septic arthritis, synovial chondromatosis, or rheumatoid synovitis are the causes of posterior interosseous nerve syndrome [4, 9, 26, 35].

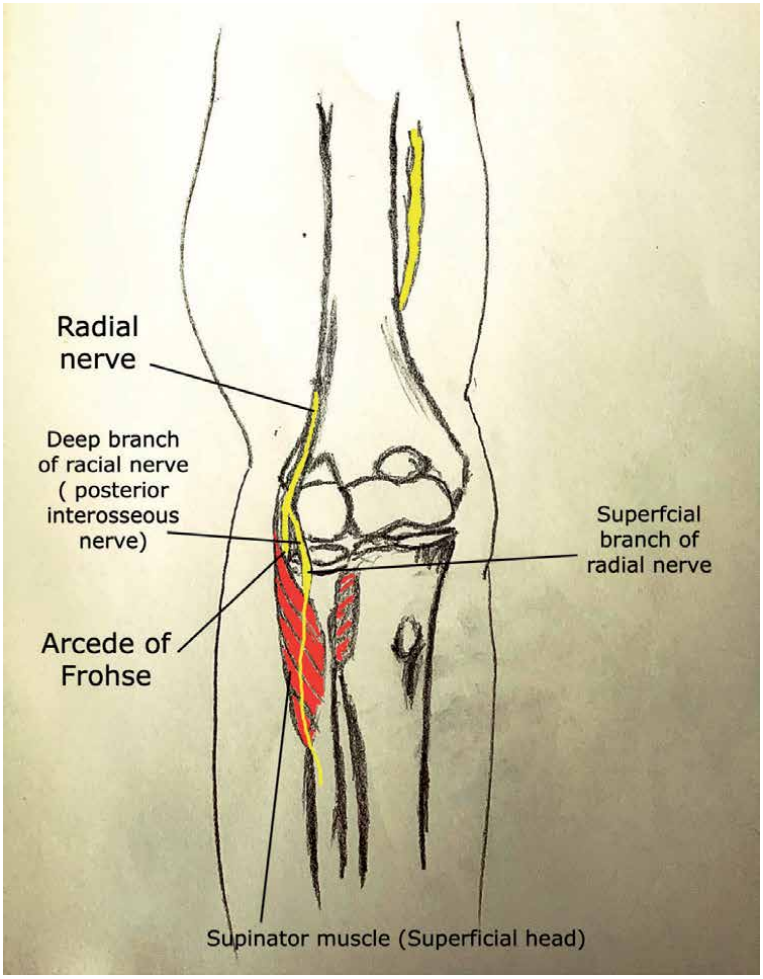

Figure 14.
The schematic drawing of the course of the radial nerve and its superficial and deep branches.

Clinical features: In PIN syndrome, wrist extensors are intact because the innervation of these muscles is at the level of the elbow joint. In PIN syndrome, paralysis develops in finger extensors, thumb extensors and abductors. There is no sensory deficit. In clinical examination, it may be mistaken for lateral epicondylitis. In lateral epicondylitis syndrome, there is pain that concentrates on the lateral epicondyle and increases with resistant extension of the wrist. In PIN syndrome, the pain is exacerbated by the resistant extension of the third finger and radiates to the lateral side of the arm. Also, resistant supination movement causes pain [1, 8, 26, 50].

2.5.5.4 Superficial cutaneous radial nerve compression (Keralgia paresthetica- Wartenberg syndrome

Anatomy: The superficial branch of the radial nerve, after separating from the radial nerve, extends distally along the radial side of the forearm deep in the brachioradialis muscle (**Figure 15**). It is superficial by piercing the fascia between the brachioradialis and extensor carpi radialis longus muscle tendons approximately 8–9 cm above the radial styloid [51, 52].

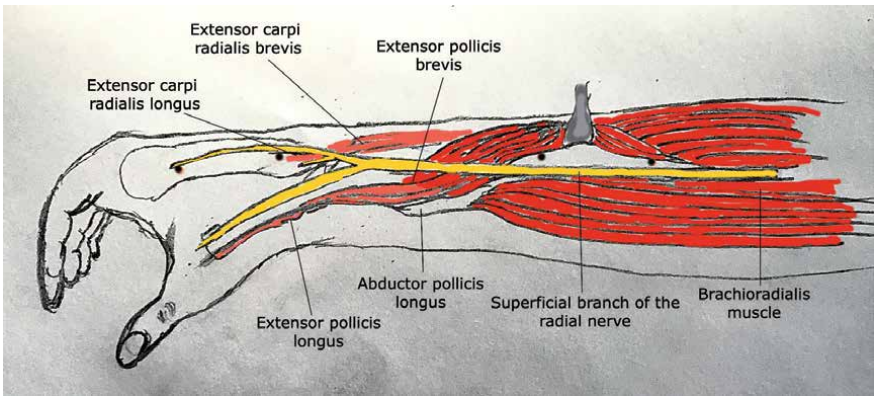

Figure 15.
The schematic drawing of the course of the superficial branch of the radial nerve in the forearm.

Description: It is a condition characterized by the compression of the superficial sensory branch of the radial nerve at the level of the wrist [1, 8, 50, 52].

Causes: Distal radius fractures, penetrating injuries, a tight watch strap or hand cuffs, a tight cast or splint, repetitive exercise (e.g. rowing), iatrogenic injury, lipoma and bony spurs are important factors causing nerve compression [1, 51, 52].

Clinical features: Patients usually complain of pain and numbness on the dorsal and lateral side of the hand. It is a pure sensory nerve so there is no motor deficits [1].

2.5.6 Impingement syndromes in the wrist

2.5.6.1 Carpal tunnel syndrome (CTS)

Anatomy: The median nerve passes between the two heads of the pronator teres muscle and reaches the forearm. In the forearm, nerve gives off branches that innervate the palmaris longus muscle, the flexor carpi radialis muscle and the flexor digitorum superficialis muscle. The palmar cutaneous branch separates from the median nerve approximately 5 cm proximal to the wrist fold. At the wrist level, the median nerve is located on the ulnar side of the flexor carpi radialis tendon and passes through the carpal tunnel [1, 16]. Carpal tunnel is lined by transverse carpal ligaments on the volar side and carpal bones on the dorsal side. In addition to the median nerve, two tendons for the 2nd, 3rd, 4th, 5th fingers (flexor digitorum superficialis and profundus) and one for the thumb (flexor pollicis longus) pass through the carpal tunnel. A total of 9 separate flexor tendon median nerves pass through the tunnel together (**Figure 16**). As the nerve passes through the carpal tunnel, it gives off motor branches that innervate the lateral two lumbricals, opponens pollicis, abductor pollicis brevis, flexor pollicis brevis muscles. Also, it provides sensory innervation of the palmar face of the radial 3,5 fingers [1, 8, 9, 35].

Description: Carpal tunnel syndrome is the most common peripheral nerve entrapment of the upper extremity. It is the compression of the median nerve under the carpal transverse ligament at the wrist level [8, 35].

Causes: Obesity, female gender, concomitant diseases (such as diabetes, pregnancy, rheumatoid arthritis, hypothyroidism, connective tissue diseases, pre-existing median mononeuropathy), repetitive wrist movements, mass lesions (eg, ganglion, lipoma, neurofibroma, fibro lipomatous hamartoma genetic predisposition and use of aromatase inhibitors are among the important causes of carpal

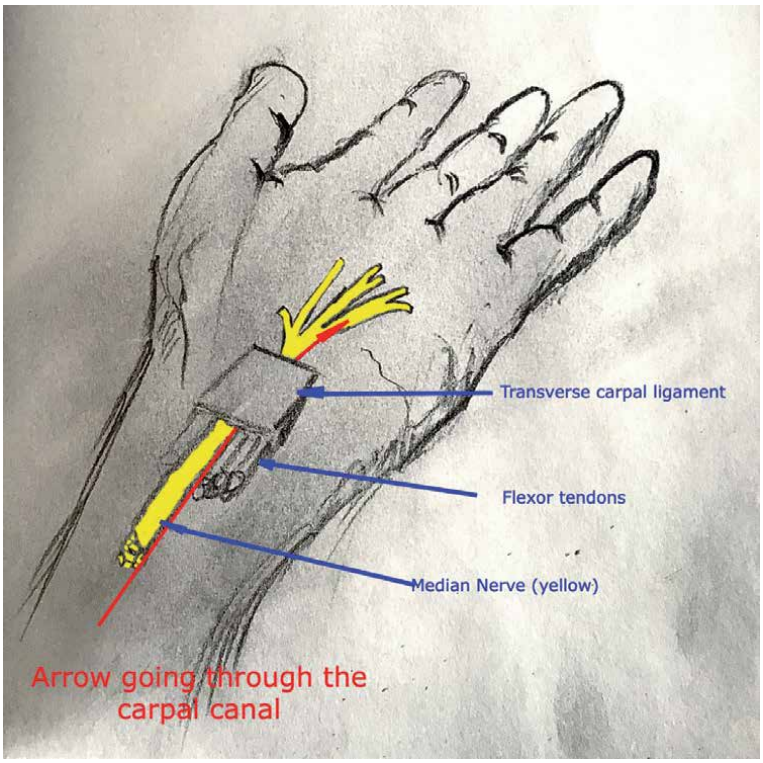

Figure 16.
The schematic drawing of the carpal tunnel and its elements.

tunnel syndrome. Also, carpal tunnel syndrome is associated with professions that require prolonged use of hand-held vibrating hand tools and long and repeated wrist flexion and extension [1, 8, 35, 53].

Clinical features: The first complaint of patients with CTS is the numbness and tingling spreading to the first three fingers of the hand, and the burning and pain sensation in the wrist. This complaint is especially aggravated at night. It has been reported that complaints were reduced by waving the hand. As the motor fibers begin to be affected over time, atrophy begins to occur in the lumbrical muscles of the 2nd and 3rd fingers, and the patient's hand weakness, incompetence (dropping something from the hand, inability to do fine hand skills) begins to develop [1, 8, 35, 53].

2.5.6.2 Guyon's duct syndrome (Ulnar tunnel syndrome)

Anatomy: After the ulnar nerve passes through the anterior part of the forearm, it comes to the wrist through the Guyon canal, a fibro-osseous tunnel located between the os pisiforme and the anchor of the os hamatum (**Figure 17**) [7, 8, 54]. The roof of the Guyon canal consists of the palmar fascia and the palmaris brevis muscle. There are pisiform and hamate bones around this canal. As the ulnar nerve passes through the Guyon canal, it divides into superficial and deep branches. After the superficial part of the nerve branches into the palmaris brevis muscle, it gives the sensory branches innervating ulnar side of the palm of the hand and all surface of the 4th finger and 5th finger. Deep part of the nerve gives branches to the hypotenar muscles. Subsequently, the deep part gives all the interosseous and branches innervating the 3rd and 4th lumbrical muscles. It ends by giving the terminal branches to the adductor pollicis and flexor pollicis brevis [16, 55].

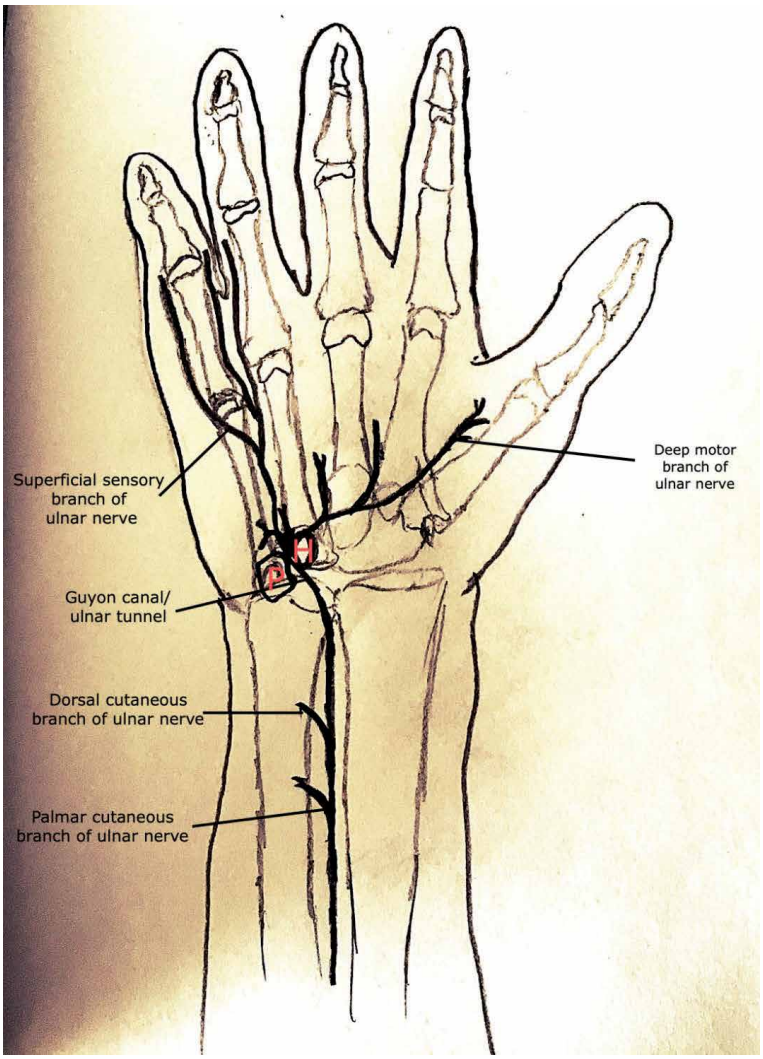

Figure 17.
The schematic drawing of the Guyon canal and ulnar nerve course inside the Guyon canal.

Description: It is characterized by compression of the ulnar nerve in the Guyon canal [1].

Causes: Using of tools, bicycle, handlebars (cyclist's palsy), crutches, using wheelchairs and work machines, osteophyte, arthritis, synovitis, ganglion, fibrous bands, subluxation of the ulnar nerve over the medial epicondyle, the presence of the Struthers arch and anconeus internus muscle, presence of os hamuli proprium, presence of an accessory abductor digiti minimi muscle and accessory or reversed palmaris longus muscle, hypertrophic flexor carpi ulnaris muscle are factors that can cause compression [1, 7, 8, 35, 55].

Clinical features: Sensory loss occurs on the palmar-ulnar side of the little finger and ring finger. Weakness and atrophy can be seen in the intrinsic muscles of the hand innervated by the ulnar nerve. Disruption of the balance between the intrinsic and extrinsic muscles of the hand causes the physiological arcs of the hand to collapse and classic claw hand deformity occurs. Froment and Wartenberg findings are positive [1, 8, 35, 55].

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Section 4

Experimental Models of Demyelination

Chapter 9

Experimental *in Vitro* and *in Vivo* Models of Demyelinating Disorders

Fereshteh Azedi, Bita Shalbafan and Mohammad Taghi Joghataei

Abstract

Experimental models provide a deeper understanding of the different pathogenic mechanisms involved in Demyelinating disorders. The development of new *in vitro* and *in vivo* models or variations of existing models will contribute to a better understanding of these diseases and their treatment. Experimental models help to extrapolate information on treatment response. Indeed, the choice of the experimental model strongly depends on the research question and the availability of technical equipment. In this chapter, the current *in vitro* and *in vivo* experimental models to examine pathological mechanisms involved in inflammation, demyelination, and neuronal degeneration, as well as remyelination and repair in demyelination disorders are discussed. We will also point out the pathological hallmarks of demyelinating disorders, and discuss which pathological aspects of the disorders can be best studied in the various animal models available.

Keywords: Demyelinating disorders, *In vitro* model, *In vivo* model

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system [1–5]. Experimental animal models are one of the useful tools because they can increase our knowledge about the central system disorders [6]. Unfortunately in MS, there is no model that can reflect all of the pathological features [7].

The use of experimental animal models, including MS models, has recently been the focus of several reports [8]. These subjects are mentioned in the ARRIVE guidelines as well [9]. Adherence to the guidelines on reporting and referring papers using experimental models of MS will be key for the translation from the bench to experimental models and eventually to the bedside of MS patients [10].

Animal models are the advantageous way to identify the immunopathological mechanisms involved in MS [11]. Animal models help scientists to develop novel therapeutic and in regenerative medicine approaches [12]. Animal models of MS have provided a beneficial platform for evaluating its efficacy in MS treatment and how this may be targeted for therapy lastly [13]. Indeed, choosing an appropriate animal model to study a complex disease like MS presents several challenges, chiefly associated with heterogeneity [14, 15]. It is well established that MS is highly

heterogeneous in terms of its genetic basis, environmental triggers, clinical course, pathology, and therapeutic responsiveness in each treatment [16]. Important factors such as genetic and environmental contribute toward MS development; however, etiology is complex and not completely assumed. Ideally, an advanced animal model has to include this heterogeneity [15, 17].

Certainly, studies in MS model need to be carefully covered the pathogenesis of the disease. A high degree of consistency between models and experimental conditions makes possible translation into therapeutic achievement [18].

Not remarkably, most of our present facts of MS have been derived from the EAE model [19]. Although EAE must be induced by artificial immunization against myelin, most therapies tested in MS patients are based on concepts derived from the EAE model, which continues to be the model system of choice. EAE models are vital for studying general concepts other than specific processes of autoimmunity; however infrequently, they predict success in clinical trials [20].

There are many mismatched aspects of pathology and immunology between EAE and multiple sclerosis. These differences are significant. For example, persistent imbalances in immune regulation are vital to the progression of multiple sclerosis, but these orders of complexity have not yet been summarized in the MS models [21]. This, in combination with a diversity of animal models that mimic specific features and processes of MS, has contributed to filling the gap of knowledge in the cascade of events underlying MS pathophysiology [22].

Until now several different EAE models have been developed, differing in the immunological reaction, inflammatory processes, and the neuropathophysiology in the CNS.

Access to up-to-date knowledge of the dynamic responses of neural cells, such as microglia in the commonly used animal models of MS, specifically the immune-mediated experimental autoimmune encephalomyelitis (EAE) model, and the chemically induced cuprizone and lysolecithin EAE models can be really helpful [23]. It is essential to elucidate the spectrum of microglial functions in these models, from harmful to protective roles, to identify emerging therapeutic targets and guide drug discovery efforts [24].

In all models, it can be observed that the harmful activation of microglial cells is in the acute stage of diseases such as encephalitis, cuprizone-induced demyelination, PCL, and FAE. However, in subacute and chronic stages, regenerative healing by microglial cells may be observed [25]. The role of T lymphocytes in EAE, CPL, and cuprizone models is important too; however, they cannot impact like microglial cells [26]. This makes these models the cleanest method for studying microglial mechanisms in innate immune systems and also all aspects of oligodendrocytes such has proliferation, differentiation, and especially the cause of remyelination [27, 28].

Briefly, this overview of the *in vitro* and *in vivo* models is commonly used to recapitulate the different faces of MS immunopathology; thus, a degree of confidence that findings with these puppets may be translated to MS therapy.

2. Fundamental pathogenesis factors change during the progression of the demyelinating disorders

As MS disease progressed, two fundamental changes occurred [29]. First, the activity of the adaptive immune system decreases leading clinically to a decrease in the incidence of clinically detectable relapses. It is currently unclear why the adaptive (and perhaps also innate) immune system becomes less active as the disease progresses, but immunosenescence likely plays an important role [30].

Second, the slow-burning degenerative process reaches a certain threshold and becomes clinically apparent.

Two possible mechanisms play a role in the retarding clinical performance [31]. One of them is a compensation of damaged or degenerated neurons by nearby neurons known as neural plasticity. Another one is the destruction of neurons without obvious clinical signs and symptoms [32]. Likely, this condition can be seen in 80% of Parkinson's patients. Many dopaminergic neurons in their brain may be lost before any clinical deficits [33]. For example, imagine that across from you is a container with 1,000 bullets. If someone removes a single bullet, it is not likely that it will be recognized. However, if only two bullets remain, most people will certainly recognize if another bullet has left the container. At the RRMS disease stage, the initial loss of neuronal structures is neither recognized by the patient nor, in the other words, does not lead to obvious clinical deficits [34]. Subsequently, during the disease, when numerous neurons are already dying at the transition phase from RRMS to SPMS, evident clinical deficits can be seen obviously [35].

3. *In vitro* models

However, it is not difficult to find primary CNS cell cultures from rodents such as mice and rats, embryonic cells, mainly neurons, and oligodendrocytes are limited.

It can be more difficult for isolating cells from adult animals and also from the human brain [36]. Because of these limitations, cell lines are used in most of the studies [37]. Among many cell lines, glial cell lines are used frequently because of a key role in the explanation of the mechanisms involved in health and disease; however, it is important to ensure the cell lines have properties like *in vivo* conditions [38].

Microglial cell activation may be seen in active demyelinating lesions. Also, it can be seen in pre-active lesions, remyelination areas, and the normal-looking white matter [39]. For finding the functions of these cells in MS, isolation of microglia from embryonic or early post-natal animals was done before [40]. However, it must be mentioned that in the field of MS and other neurodegenerative disorders, using young animal cells may not be relevant to study chronic diseases that happened in older animals and humans [41, 42]. Thus, few studies are using aged microglial cells isolated from adult animals such as rhesus monkeys and humans. Notably, because of many limitations such as ethical aspects, using cells isolated from post-mortem are often in humans and primates [42, 43].

An important issue with respect to the use of microglia cell cultures is what it tells us about the pathogenesis of MS. Based on previous studies, primary human microglia cultures derived from MS brain tissue versus healthy brain have the major advantage of revealing pathways involved in the disease process [44]. Another major problem is microglial cells like other cells of the innate immune system, which reacts quickly to any danger or foreign signals. Therefore, the use of fast isolation methods for revealing the initial trigger of microglia activation is critical [45]. Studies using a detailed transcriptomic analysis in the cuprizone animal model of MS found that in the early stages of demyelination, a microglia phenotype supportive of regeneration is observed [46]. It stays to be determined if this is also observed in tissues affected by multiple sclerosis, which are normally available only after a very long continuance of the disease. Nevertheless, multiple sclerosis lesions disappear throughout the disease and early stages of lesion development (microglia clusters considered pre-active lesions) are honored even after a long continuance of the disease. Detailed studies using animal models may provide important facts about the role of microglia in lesion development in MS [47].

Oligodendrocytes are diligent in the production of myelin in the CNS [48]. In CNS tissues, various development stages of oligodendrocytes can be observed, including the pre-progenitor, progenitor, pro-oligodendrocyte, and juvenile oligodendrocytes. Each of these steps can be identified *in vitro* and *in vivo* through the expression of several different molecules such as proteins involved in myelin structure and production. It can be possible to maintain primary rodent oligodendrocytes *in vitro* for up to several weeks by several methods [49]. According to previous findings, when these cells proliferate and differentiate depending on the culture medium *in vitro*, the features of these cells may change during subcultures. Thus, re-checking the characteristics of passaged cells is very important [50].

In general, isolation of primary oligodendrocytes is dependent upon their ability to not adhere to culture plates. This feature has benefits because by gently shaking isolated cells from the CNS, microglia and adherent atrocities can be separated from floating oligodendrocytes [51]. A disadvantage of the primary cell culture of oligodendrocytes is that they are usually only available in small numbers. However, mature oligodendrocytes can be obtained when glia progenitors are cultured in serum-free media or by differentiating stem cells [52].

Other important cells that change with MS include astrocytes. In the injured brain, the shape of astrocytes turns into hypertrophic form and the scar tissue as typical of chronic MS lesions generate [53, 54]. When astrocytes are damaged, they are at the risk of losing the ability to maintain the blood–brain barrier (BBB), thus contributing to additional damage [55]. Astrocytes also contribute to the repair process by secreting growth factors, so they have the ability to promote regeneration [56, 57]. By now, several human and animal cell lines are available, as well as primary astrocyte cultures. Primary astrocyte cultures often grow slowly. Therefore, it is the advantage of astrocytes not only being suitable for repeated subcultures, but also suitable for cryopreservation [58]. Many studies using the cell lines of astrocytes are available. Usually, they have been derived from rodents or isolated from human brain tissue with astroglioma. A weakness of astrocytic cell lines is that they respond in a different way in comparison with primary cultures [59]. Several protocols allow obtaining primary astrocytes from adult tissues or post-mortem fetal as well as from biopsies or resected brain tissue in neurosurgery cases. While primary human astrocytes are attractive to culture, care must be taken to ensure the adequate removal of microglia that frequently contaminate primary astrocyte cultures and may influence responses in culture [60].

In MS research, the increasing awareness that axonal damage and neurodegeneration contribute to the progression of the disease has prompted researchers to use neuronal cells. One ordinary cell line is the neuroblastoma cell line is SH-SY-5Y that can be differentiated with retinoic acid (RA), while the HCN and the NT2 cell lines are differentiated with brain-derived growth factor (BDNF). But it has to be considered that these cells cannot express many markers of mature neuronal cells. These cell lines are also slow to proliferate *in vitro and* require expensive growth factors [61, 62]. Absolutely, it looks like finding more neuronal cell lines is necessary for a better MS search.

4. *In vivo* models

The MS *in vivo* experimental models can be separated into three classes:

1. Auto-immune or inflammatory patterns, such as examples of experimental allergic encephalitis (EAE) and viral patterns.

2. Demyelinating or remedial models, including models for chemical damage induced by cuprizone, lysolecithin and ethidium bromide.

3. Transgenic models to more precise reproduce the key pathological diseases [63, 64]

4.1 Experimental autoimmune encephalomyelitis (EAE)

EAE is a spectrum of neurological disorders. EAE can be induced in laboratory animals such as rats and mice after immunization with CNS antigens emulated in an adjuvant to enhance immune response [20].

Usually, in these models, purified myelin, recombinant proteins, or peptides related to encephalitogenic myelin protein are applied. Notably, myelin lesions and inflammation in MS are common features; however, neurodegeneration is a major characteristic as well. Therefore, the secondary progressive EAE was developed with main characteristics such as cortical demyelination, experimental inflammatory neurodegenerative, and spastic diseases [22, 65].

The clinical course of EAE depends on several factors, including the immunization protocol, the antigen, and age, gender species, and strain of the animals. With the active immunization protocol, the first signs of neurological illness are usually weight and activity loss and can be observed between 10 and 17 days. When the adoptive transfer method is used, signs are seen a little earlier, starting 5–7 days after cell transfer [21, 24].

The EAE clinical signs are typically rated based on a muscle force scale (0 to 5) that reflects increasing degrees of paresis, with grade zero being normal and graded 5 being moribund. There are other scoring systems depending on the species used and focus on other clinical signs than just paresis (muscle weakness). Neurological disease can also be monitored using a rotor rod to measure dexterity, and as well as by monitoring behavioral changes [66].

4.2 Toxin models

A further possibility of investigating demyelination with subsequent remediation is the use of toxin models [47]. In these models, demyelination is induced after focal application or systemic administration of the toxin. Copper-chelating cuprizone is the most common toxin used to induce demyelination in the CNS using systemic administration [28].

Cuprizone or oxalic acid bis cyclohexylidene hydrazide is a selective and sensitive copper-chelating agent. Shortly after its discovery, it was used to detect copper in serum. W. Carlton was one of the first ones to systematically study and describes disabling changes in cuprizone-fed animals, including sponginess, edema formation, hydrocephalus, demyelination of the central nervous system, and liver damage [46]. Based on Carlton's findings, we can find several studies using 6–9-week-old mice with a diet containing 0.2–0.3% cuprizone. In older animals, the concentration of comparison must be high in the feeding to guarantee adequate demyelination. In addition, vulnerability to cuprizone that depends on the strain has been reported. For example, there is a difference in the anatomical distribution of demyelinated foci between SJL and C57BL/6 mice. Based on previous studies, we cannot observe demyelination at the brain midline within the corpus callosum in SJL mice; however, demyelination can be seen immediately from the lateral part of mice brain [47]. Therefore, focusing on these variables can be very important before starting any studies.

4.3 Viral models

Viral myelin damage models have been used to investigate the relationship of viruses in multiple sclerosis, and they have led to major breakthroughs in our understanding of the pathology of multiple sclerosis [67]. Both genetic and environmental factors have been implicated in MS, with greater importance attributed to the latter [68].

A possible role of viruses in the pathology of MS is suggested by epidemiological studies by the detection of viral antigens and virus-specific antibodies in the greater part of MS patients [69]. Several mechanisms can explain how viruses can induce demyelination and also involved in MS [70]. Damage may consequence either from an effect on neurons directly, known as a secondary event (the so-called inside-out model), or from a direct attack on myelin, in which case neurons die due to the lack of trophic support by myelin (the so-called outside-in model).In brief, the virus can damagethe CNS through direct infection of oligodendrocytes, which can be seen in progressive multifocal leukoencephalopathy and lately in MS patients following immunomodulatory therapies [71]. Moreover, viruses can irritate infected oligodendrocytes to attack the CNS. Through these direct effects, virus infection can affect myelin and neurons *via* multiple pathways [72].

4.3.1 Theiler' s murine encephalomyelitis virus (TMEV)

Theiler's Murine Encephalomyelitis Virus, first named by Max Theiler, is a natural pathogen of black eyes, causing paralysis and encephalomyelitis. Unlike Semliki Forest virus (SFV), Theiler's murine encephalomyelitis virus infection causes clinical neurological disease in immunocompetent mice, as well as atrophy of the brain and spinal cord. In addition, myelin damage is seen in bare/bare athymic mice, indicating a direct effect of viral infection independent of immune response [73].

4.3.2 Murine hepatitis virus (MHV)

Like TMEV, MHV is a natural pathogenic agent of mice that infects all types of CNS cells (neurons, astrocytes, and ...). Specific strains of MHV, such as John Howard Mueller (JHM), have a distinctive tropism of CNS leading to severe acute encephalitis [74]. Strains with a less pronounced neurotropism, such as the gliatropic MHV-A59 strain, generally establish a persistent CNS infection, contributing to chronic inflammation and demyelination. Mice inoculated intra-nasally or intra-cerebrally with the JHM virus or MHV-A59 strains mount a robust immune response leading to an influx of immune cells that largely clear the virus, although low-level viral infection persists in animals surviving from the acute infection [75]. In contrast to TMEV, infected MHV-susceptible mice develop a single major symptomatic episode such as hind limb laziness, ataxia, and paralysis, most of which recover. Demyelination begins about a week after infection, with the peak at week 3–4, after which lesion repair and remyelination can occur [76].

4.3.3 Semliki Forest virus (SFV)

SFV is a neurotropic alphavirus of the family Togaviridae that infects neural cells in the CNS such as neurons and oligodendrocytes. In adult C57BL/6 and BALB/c mice, the virus is largely cleared from the CNS by 6 days post-infection. Demyelination peaks around day 14 and subsequently wanes, with sporadic and mild clinical symptoms [77]. The CNS demyelination observed in SFV-infected mice appears to involve T cells, as demyelination does not occur in nude or SCID

mice. Indeed, in BALB/c mice, depletion of CD8+ but not CD4+ T cells abolishes demyelinating lesions. Demyelination may also occur following cytolytic damage of virus-infected oligodendrocytes. In this model, in C57BL/6 mice, molecular mimicry may also take on a role in demyelination, as infected mice exhibit proliferative T cell responses to myelin basic protein (MBP), and antibodies (Abs) reactive to MBP and myelin oligodendrocyte glycoprotein (MOG). Indeed, it was suggested that demyelinating lesions are mainly made by antibody responses, which have cross reaction to MOG and the SFV E2 protein [78].

4.3.4 Sindbis virus (SV)

The VS infection in LSU mice is another demyelinating model. This model has not been extensively studied by investigators; however, recent findings indicate that pathogenic infection may cause autoimmune disease [79]. Infected LSU mice develop EAE-like palsy that begins at 6 dpi and lasts up to 8 weeks after infection. Treatment with cyclophosphamide improves the signs of neurological deficits despite the increase in CNS viral load, indicating that paralysis in these mice is mediated by the immune response. CNS lymphocytes taken at 7 dpi are specific to VC, but not to MBP. Interestingly, MBP-specific T cell and Ab responses are found in the peripheral tissues at 8-week post-infection, indicating that anti-myelin responses arise due to bystander damage *via* epitope spreading. The brief common period from SV infection to first neurological deficit indicates that the demyeliationg process is not the primary cause of paralysis, but can contribute to chronic illness [80].

4.4 Transgenic, mutant, and parabiotic mice

The accessibility of mutant, transgenic, and probiotic experimental animal models could increase our knowledge about the mechanisms of myelin and axonal damage [81]. These models include mutant mice in which defects in myelin assembly occur. Another one is transgenic mice with deleted or inserted genes coding for immune components, and the other one is conditional knockout mice with genes manipulations in mature animals [82]. The generation of parabiotic mice has come about recently. The role of specific myelin proteins in myelin synthesis and remyelination has been examined in mutant mice in which the CNS myelin is affected. These include the Shiverer mouse in which the MBP gene is duplicated and inverted. Also, these consist of the Rumpshaker mouse with mutated proteolipid protein (PLP) Plp1 and the Jimpy mouse with the PLP gene mutation. These genetic mutations result in dysmyelination due to, for example, oligodendrocyte apoptosis and lastly neurodegeneration because of myelin damage. The importance of the role of immune responses in multiple sclerosis has led to the development of transgenic mice by focusing on myelin proteins or specific immune molecules. MOG-knockout mice have no recognizable phenotype. However, the use of its for EAE studies has revealed a major role for autoimmunity to MOG in chronic EAE in both mice and marmosets [70].

The parabiotic model is the act of living side-by-side [83]. Parabiotic studies involve suturing two mice together so blood vessels can connect, creating mice that share a common blood supply. Thus, the effect of the treatment of one mouse can be considered in the other mouse. Previous studies by using irradiation and separation of parabiotic mice indicated the importance of infiltrating monocytes in the induction of clinical signs of EAE [84]. Such surveys have been performed using transplantation of donor cells, although it has often been impossible to distinguish between donor cells and activated microglia from the host. Another study using

isochronic (same age) or heterochronic (same age) parabiotic mice indicates that exposure of young mice to the blood flow of old mice interferes with neurogenesis. This parabiotic study revealed age-related chemokines, suggesting the presence of rejuvenation factors. Heterochronic parabiotic mice are useful for understanding this point that remyelination is not merely more efficient in juvenile mice, but also some factors from juvenile mice can even restore the potential of remyelination in old mice [85].

5. Conclusion

There is no one specific model showing all the factors involved in the pathogenesis of multiple sclerosis, so the researchers attempt to acquire a spacious range of examples that can imitate various MS features. Extremely, the development of alternative and mixed models will contribute to an improved understanding of multiple sclerosis and its treatment. With the help of animal models, information on response to treatment can be extrapolated. The development of models better able to reproduce the pathological changes of MS constitutes the beginning stage in the development of novel treatments; however, we are most likely to achieve a genuine understanding of MS through data from patients. The existing examples have shown useful in the evolution of MS treatment, and further integration of these examples will help further our understanding of the etiology.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 10

Pericytes of the Brain in Demyelinating Conditions

Stavros J. Baloyannis

Abstract

The pericytes play a very important role in the central nervous system (CNS), concerning the formation of the functional neurovascular unit, serving as a substantial component in the development and maintenance of the stability of the blood-brain barrier (BBB). Besides, as pluripotent cells of neuroectodermal origin, the pericytes participate in autoimmune reactions and modulations, controlling the penetration of immune cells via BBB and playing an active role in lymphocytic trafficking and functional regulation, via cytokine secretion and activation. In demyelinating conditions, they participate in the restoration of the myelin sheath by modulating oligodendrocytes and stimulating the differentiation of oligodendrocyte progenitors. In the experimental model of allergic encephalomyelitis (EAE), electron microscopy reveals the proliferation and the morphological alterations of the pericytes as well as their interactions with endothelial cells and astrocytes, thus underlining the crucial role that pericytes play in the integrity of the BBB and the immune reactions of the CNS.

Keywords: pericytes, demyelinating conditions, electron microscope, BBB, EAE

1. Introduction

Multiple sclerosis (MS) is among the most enigmatic disorders of the central nervous system, affecting a substantial number of patients, at any age from childhood to senility, inducing a large spectrum of physical and mental disability in a considerable number of them, with a high prevalence in Europe and North America [1].

The clinical diagnosis of multiple sclerosis is not always an easy task, due to the polymorphic and multidimensional pattern of the clinical manifestations of the disease, which might be associated with other disorders.

The phenomena and the severity of the disease would be evaluated based on the criteria of the expanded disability status scale (EDSS) [2].

The pathogenesis of MS, which has been considered as a chronic immune-mediated disorder of the central nervous system (CNS) [3], has to be further clarified, although some risk factors such as genetic predisposition, viral, bacterial, or parasitic infections [4], climatic, environmental, and dietary factors [5], head trauma, and physical or psychological distress may play a substantial role in the puzzling etiological background of the disease.

Besides, the multidimensional underlying pathological mechanisms of multiple sclerosis, involving numerous cell interactions, molecular reactions, and activation of autoimmune responses via a multitude of signaling factors, result in inflammatory

infiltration, demyelination, gliosis, and axonal damage, which compose a very complicated labyrinthine pattern, causing a reasonable difficulty in the effectivity of any targeted therapeutical approach of the disease [6].

Among the many cellular components, which participate actively in the process of demyelination and remyelination, during the continuous neuropathological alterations and interactions in the brain and the spinal cord, during the long course of multiple sclerosis, the pericytes being heterogeneous cells [7] described by Rouget, originally called Rouget cells [8] and named pericytes by Zimmermann [9], seem to play a substantial role at any stage of the disease.

It is well known that brain pericytes are pluripotent progenitor cells of neuroectodermal origin [10, 11], which are located mostly around the blood vessels (peri, περι = around) and serve as substantial components of the blood-brain barrier (BBB), being in direct contact with the endothelial cells, sharing a common basement membrane with them, and developing many functional interactions with endothelial cells, astrocytes, perivascular microglia, and macrophages [12].

It is important that the pericytes contribute to the formation of the functional neurovascular unit (NVU), which is composed of endothelial cells, pericytes, astrocytes, and neurons, and serve as a crucial structure for the integrity and functional stability of the central nervous system [13, 14]. The pericytes participate also in the development of the wall of small vessels, such as pre-capillary arterioles, capillaries, and post-capillary venules, enveloping the endothelium and being separated from them by a basement membrane (BM). Over most, the fact that the pericytes play a crucial role in the function of the blood-brain barrier [15] is of particular importance, particularly in the development of the tight junctions and in the vesicle trafficking in the endothelial cells, controlling the permeability of the BBB and participating effectively in its reconstruction and remodeling, in cases of anatomical disruption or functional decline, contributing therefore essentially in the stability of brain homeostasis [16].

A substantial body of evidence revealed that inducible pericyte knockdown in experimental animals resulted in disruption of the blood-brain barrier and rapid loss of neurons [17, 18].

It is important that the pericytes do frequently migrate in the neuropile space and even proliferate into different cellular types participating in a multitude of cell interactions [19].

Besides, pericytes participate in autoimmune reactions and modulations, mediating the neuroinflammation [19], and controlling the penetration of immune cells via BBB, playing an active role in lymphocytic trafficking and functional regulation via cytokine secretion and activation [20–22], and eventually contributing in glial scar formation [23].

The fact that pericytes are involved in the remyelination of the CNS, by modulating oligodendrocytes and stimulating the differentiation of oligodendrocyte progenitors [24], is of substantial validity.

The density of the pericytes varies from tissue to tissue, being the highest in the CNS, apart from the retina [25]. However, their number is not definitely stabilized, given that they could differentiate into other cell types, including glial cells and neurons under various conditions, in reaction to tissue injury [26].

For a further observation and detailed analysis of the gradual neuropathological phenomena and the cellular interactions, which occur in multiple sclerosis, animal models have been created by active immunization of susceptible recipients [27]. Among them, the experimental allergic encephalomyelitis (EAE) is the most frequently used animal model [27], which has been induced in genetically susceptible animals such as rats, mice, guinea pigs, rabbits, and monkeys by injecting

compounds that would stimulate the immune system, resulting in developing inflammatory perivascular infiltrates in the CNS [28].

In the majority of the experimental models, the injected immunogenic factor is derived from CNS proteins such as myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG). The injected animals may develop neurological manifestations due to creation of inflammatory foci and demyelination in random areas of the CNS, in analogy to MS [29, 30].

Among the cellular components, the pericytes [31], the microglial cells, and the perivascular macrophages (PVM) [32] may play a substantial role in mediating neuroinflammation in the CNS in the EAE, as well as in MS and other autoimmune neurological conditions [32–34].

In the present study, we attempted to study the ultrastructural alterations of the pericytes around the capillaries and the venules of the brain in animals, which developed experimental allergic encephalomyelitis, knowing that there are some substantial limitations, due to the different pathogenetic mechanisms of the EAE, in correlation with MS [35].

2. Material and methods

2.1 Material

Sixty adult Lewis rats (AgB1) of both sexes (30 male and 30 female animals), of 150–200 mean body weight, were immunized by slow injection in their hind footpads of 50 μm of guinea pig myelin basic protein, emulsified in Freund's complete adjuvant.

All the rats were clinically examined and scored daily following the immunization. The first clinical findings appeared between the 10th and 12th day following the injection. On the 18th day after the immunization, all the clinical manifestations of the animals were quantified and scored based on a 0–5 disease severity scale, where 0 means no clinical findings, 1 means loss of the tone of the nail, 2 means weakness of the hind limb, 3 means paralysis of the hind limb, 4 means paralysis of the hind limb and severe weakness or paralysis of the forelimb, and 5 means expiring condition or death [36, 37].

From the 60 immunized animals according to the final clinical evaluation, 2 of them were scored 0, 12 were scored 1, 10 were scored 2, 22 were scored 3, and 14 were scored 4. No one died.

Then, under ether anesthesia, all the rats were sacrificed, by perfusion with 200 ml buffer solution (buffered physiologic saline) followed by 250 ml of Sotelo fixing solution [38] containing 2.5% glutaraldehyde, 1% paraformaldehyde in 0.2 cacodylate buffer, adjusted at pH 7.35. For the perfusion, a Holter pump (flow 25 HPM) was used.

After the fixation, the skull of each animal was opened as well as the spinal canal, and the brain and the spinal cord were quickly removed and immersed in newly prepared Sotelo solution at 4°C.

2.2 Method

Coronal sections of the brain hemispheres were performed. The brain stem, the cerebellum, and the spinal cord were cut into sections of 2 mm thickness. Samples were taken under a dissecting microscope and immediately processed for electron microscopy.

All the specimens were immersed in newly prepared Sotelo fixing solution, for 3 h, then they were postfixed in 1% of osmium oxide for 30 min at room temperature and dehydrated in graded alcohol solutions and propylene oxide. After the dehydration, the specimens were embedded in Araldite mixture.

Semi-thin sections were performed on a Porter-Blum microtome and stained with 1% toluidine blue. Thin sections of silver-gray inference color were cut in a Reichert ultratome, mounted on bare 400 mesh grids, contrasted, with uranyl acetate and lead citrate, and studied in an electron microscope Zeiss 9As.

Besides, multiple sections of the brain hemispheres, the brain stem, the cerebellum, and the spinal cord, were prepared for histological examination. Thus paraffin-embedded sections were stained with hematoxylin and eosin and were serially studied in the light microscope at a magnification of 25× and 100×.

The histological diagnosis of the experimental allergic encephalomyelitis was based on the identification and quantitation of the perivascular infiltrates of mononuclear cells and lymphocytes in the brain, the cerebellum, and the spinal cord.

3. Results

3.1 In light microscopy

The histological examination of the H and E stained sections revealed a substantial number of perivenular and pericapillary infiltrations in the brain hemispheres, the brain stem, and the cerebellum of the animals, with the greatest amount of infiltrations seen in animals, which were scored 4 and 5. The spinal cord was seriously involved showing the highest number of perivascular infiltrates in all animals. No infiltrations were observed in animals scored 0.

The semi-thin sections of Araldite embedded tissue, which were studied in light microscopy revealed, besides the perivascular infiltrates, alterations of the myelin sheath of the myelinated axons in the brain hemispheres, the cerebellum, and extensively in the spinal cord in animals scored 4 and 5.

3.2 In electron microscopy

By electron microscopy, the pericytes were seen in the wall of the brain capillaries, around the endothelial cells (**Figure 1**). They are characterized by their large round or ovoid nucleus, with rough distribution of the chromatin, the plenty of mitochondria and ribosomes perikaryon, and the basal lamina, which surrounds the cell body. They interacted with the endothelial cells, which create gap junction, surrounding them.

A substantial proliferation of pericytes was noticed in the spinal cord and the cerebellum around the capillaries and the venules, escaping the basal lamina (**Figure 2**) particularly in animals scored 4 or 5. All of them extend long processes, on the one hand surrounding the wall of the blood capillaries and on the other approaching the astrocytes in the perivascular space.

Morphologically, the majority of the pericytes and the endothelial cells demonstrated aggregations of many small mitochondria around the nucleus, dilatation of the cisternae of Golgi apparatus, and large lysosomes (**Figures 2** and **3**). The nucleus of the activated perivascular pericytes was mostly round or ovoid, distinguished clearly from the very elongated nuclei of the endothelial cells (**Figure 4**). The nucleus of the perivascular pericytes demonstrated, as a rule, a rough distribution of heterochromatin in the periphery. The perikaryon included large number of small round mitochondria, with fragmentation of the cristae in the majority of

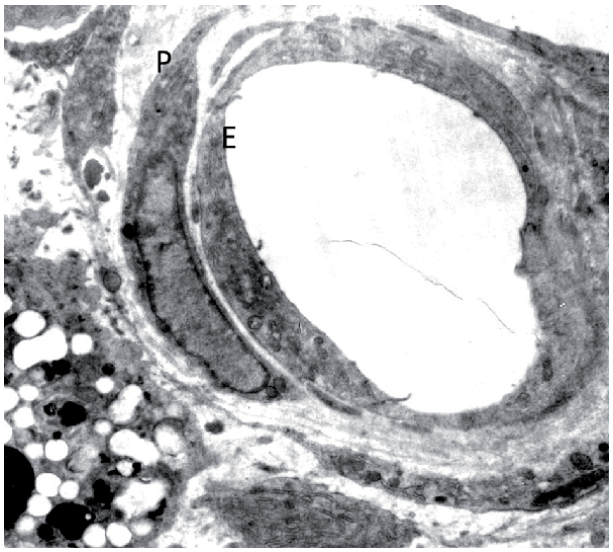

Figure 1.
Pericyte (P) in the wall of a brain capillary near the endothelial cell (E). Electron micrograph (mag. 35,000×).

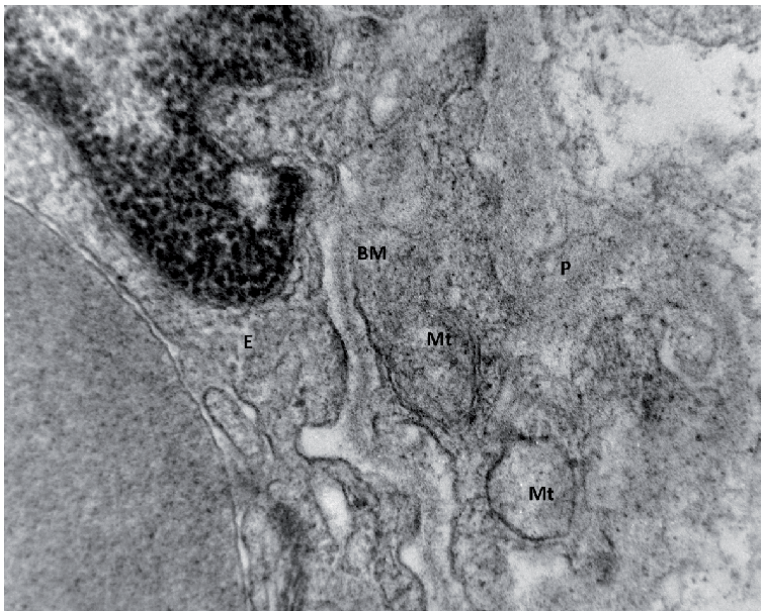

Figure 2.
Pericyte escaping the basal membrane (bm) around a brain capillary. The mitochondrial alterations are obvious. Electron micrograph (mag.128,000×).

them. A substantial number of endothelial cells demonstrated dilatation or disruption of the tight junctions (**Figure 5**).

Many capillaries showed marked perivascular edema and accumulation of lymphocytes and monocytes. It was noticed that pericytes in the neuropile space were intermixed with astrocytic processes (**Figure 6**).

A large number of pericytes demonstrated an increased number of pinocytotic vesicles, large lipid granules, and mitochondrial alterations, and marked dilatation of the cisternae of the smooth endoplasmic reticulum (**Figures 2** and **3**).

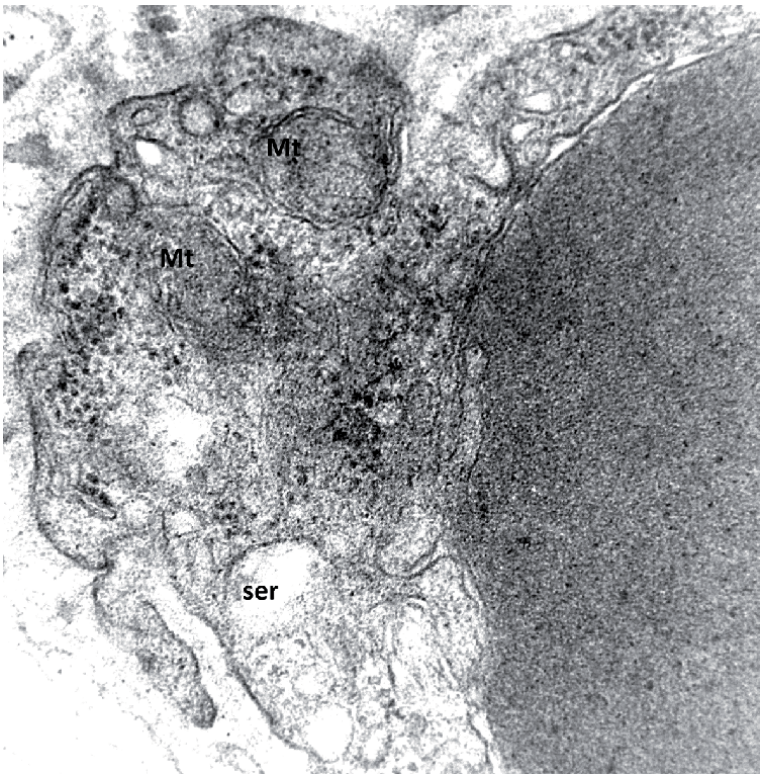

Figure 3.
Alterations of the mitochondria and dilatation of the smooth endoplasmic reticulum (ser) in an endothelial cell of the wall of a brain capillary. Electron micrograph (mag. 128,000×).

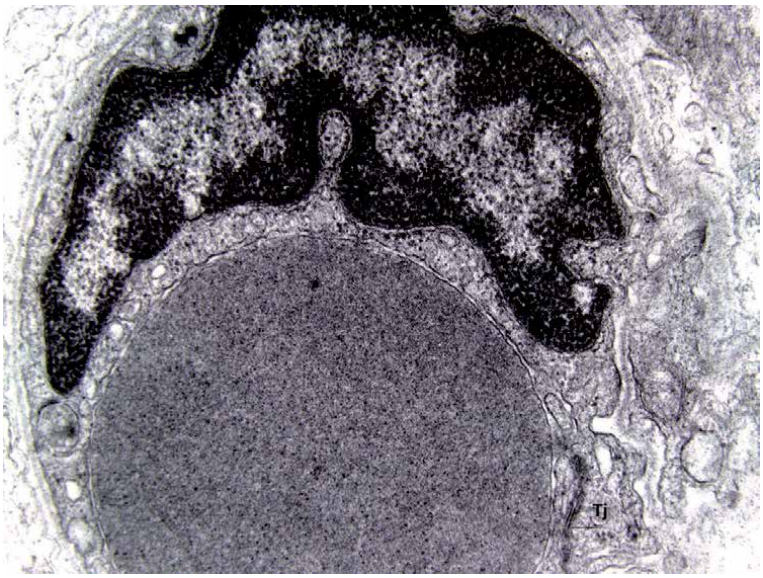

Figure 4.
An endothelial cell of a brain capillary, showing abundant peripheral accumulation of heterochromatin and disruption of the tight junction (Tj). Electron micrograph (mag. 35,000×).

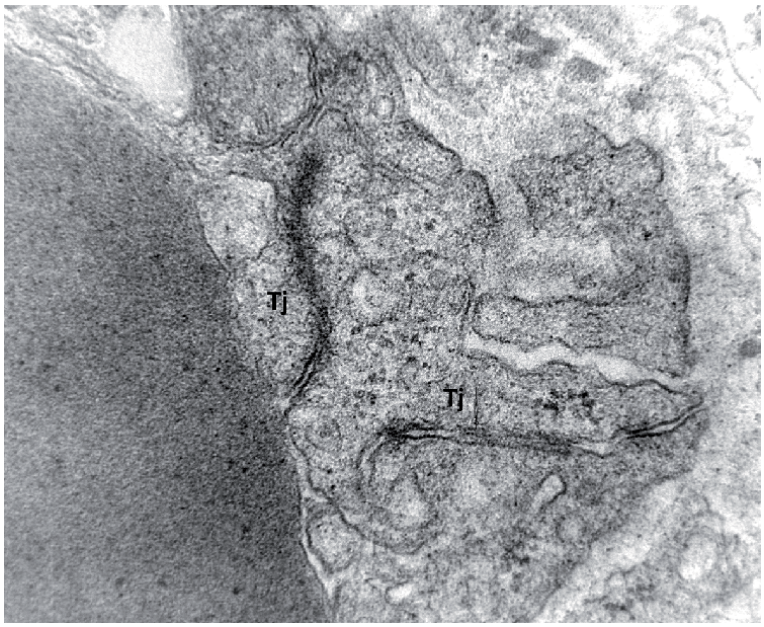

Figure 5.
Disruption of the tight junctions (Tj) of a brain capillary. Electron micrograph (mag. 128,000×).

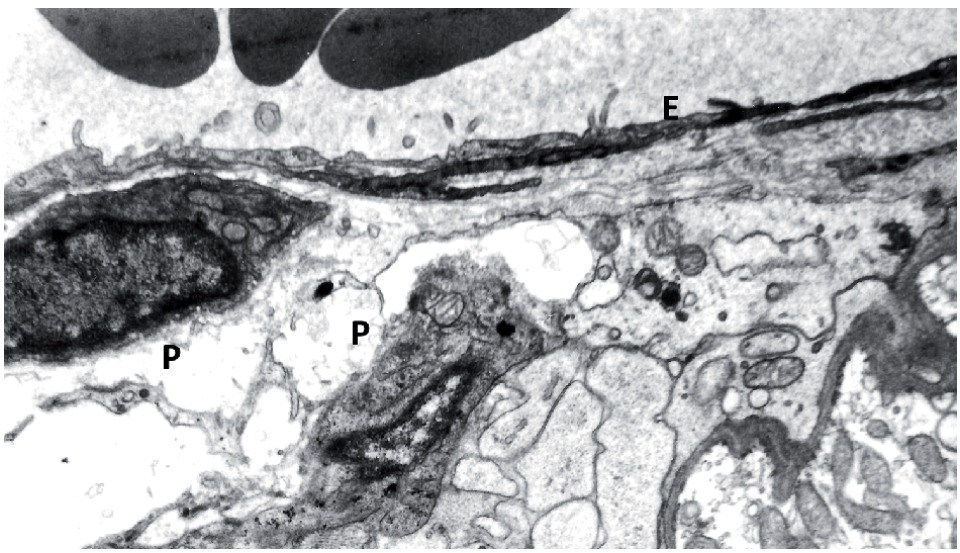

Figure 6.
Pericytes (P) in the neuropile space around the endothelial cell (E) of a dilated brain capillary. There is a marked perivascular edema. Electron micrograph (mag. 35,000×).

4. Discussion

Pericytes are polymorphic perivascular cells, which collaborate with the endothelial cells for the regulation of the blood–brain barrier's permeability [39]. A substantial body of evidence, derived from morphometric observations in light

and electron microscope, revealed that the ratio of pericytes to endothelial cells in the majority of the structures of the central nervous system is approximately 1:1 [39]. However, not all of the perivascular cells are pericytes, given that some of them are macrophages or adventitia cells [40], presumably derived from the pericytes, which as pluripotent cells can generate other cell types, to maintain the brain homeostatic equilibrium [22].

In MS, the proliferation or the degeneration of the pericytes associated with dysfunction or disruption of the blood-brain barrier is one of the initial neuropathological phenomena [41], triggering a cascade of inflammatory reactions and cellular interactions.

In the model of the experimental allergic encephalomyelitis, alterations of the blood-brain barrier have been described in electron microscopy by many authors [42–44]. The role of the pericytes in inducing those alterations may be crucial, given that perivascular pericytes regulate endothelial transcytosis, which would increase the permeability of the blood-brain barrier [45].

In the model of pericyte-deficient mice, an increased expression of leukocyte adhesion molecules has been described in association with polarization defect of astrocyte end feet in the vessels of the brain, underlining the importance of the pericytes for the integrity of the blood-brain barrier [46].

On the contrary, the proliferation of the pericytes suggests that they participate in the immune reactions of the brain, a fact that is noticed and described also in multiple sclerosis [21]. It was noticed that the pathological alterations in experimental allergic encephalomyelitis mimic to some degree, in many aspects, the morphological alterations, which occur in multiple sclerosis [47, 48].

Many histological observations revealed that the morphology of the pericytes varies considerably in the various structures of the brain in normal and pathological conditions. Among other conditions, proliferation of pericytes was described in early cases of Alzheimer's disease, associated with disruption of the BBB [49] as well as in traumatic brain injuries [50].

Although many markers have been used for the identification of pericytes in various conditions, none is unanimously accepted as the precise and definite one, given that pericytes retain the multipotential properties of stem cells [51] or express a macrophage-like function [52].

The proliferation of the pericytes around the capillaries and the venules in the central nervous system has been observed mostly at the initial stages of the inflammatory conditions, autoimmune reactions, and degeneration of the brain, given that as the process advances, the pericytes further migrate into the neuropile space, and the ratio between them and the endothelial cells declines consequently [53].

In many pathological conditions, the pericytes contribute to the restoration of the BBB substantially, either by their contact with the endothelial cells or through proper signaling [54, 55], a fact that is beneficial for the establishment of the brain homeostasis.

A reasonable therapeutic approach to multiple sclerosis may be attempted by enforcing the interactions between pericytes, endothelial cells, and astrocytes, which may result in the restoration of the blood-brain barrier [56, 57].

It would also be emphasized that the observation that activated pericytes may contribute substantially to the differentiation of the oligodendrocyte progenitors, enabling consequently the restoration of the myelin sheath, and the protection of the axons is of substantial importance for finding an escape from the labyrinth of the disease [58]. This novel role of pericytes may open new therapeutic horizons in the field of demyelinating conditions [59, 60], as a catharsis from the drama of multiple sclerosis.

5. Conclusions

1. Pericytes play a very important role in the formation and mentainance of the blood-brain barrier (BBB), as a substantial component of the neurovascular unit.

2. Pericytes participate actively in the autoimmune reactions of the central nervous system (CNS), having the capacity to interact with oligodendrocytes and astrocytes and even to generate other cell lines.

3. In the experimental model of multiple sclerosis (MS), the experimental allergic encephalomyelitis (EAE), the electron microscopy shows clearly the proliferation of the perivascular pericytes, their migration into neuropile space, their morphological alterations, and even their collaboration with endothelial cell, for the restoration of the disrupted BBB.

4. Activated pericytes may contribute to the differentiation of the oligodendrocyte progenitors, a fact that may enable the restoration of the myelin sheath and increase the axonal protection.

5. Therapeutic regimes protecting the pericytes in the early stages of demyelinating conditions may open new promising horizons in the treatment of multiple sclerosis.

Conflict of interest

The author declares no conflict of interest.

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Demyelination disorders are among the most frequent neurological conditions. Types of these disorders include multiple sclerosis, Guillain Barré syndrome, diabetic peripheral neuropathy, entrapment neuropathies, and others, all of which can result in serious physical incapacity and diminished quality of life. This book examines various aspects of demyelination from clinical, diagnostic, and therapeutic points of view. Chapters address different types of demyelination diseases, their associated mechanisms, and pharmacologic and nonpharmacologic treatment approaches, among other topics.

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