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DOCTORALE THESIS

CLINICAL AND IMAGING CORRELATIONS AND COPING STRATEGIES IN MULTIPLE SCLEROSIS

-ABSTRACT-

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CHAPTER 1. THEORETICAL ASPECTS

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system, which causes demyelination and axonal damage. Apart from the fact that its cause is unknown, multiple sclerosis is characterized by the presence of demyelination areas (highlighted at magnetic resonance imaging) as well as by a variety of neurologic manifestations.

It is the most common non-traumatic affection among young adults, causing major neurological disability, especially in Europe and North America.

The disease occurs in young adults aged between 20-40 years old. It can also occur in the case of children or after the age of 50 years old. Women are 2-3 times more often affected by it than men.

Emphasizing the complex relation between the environmental and genetic factors which lead to the development of MS, studies suggest that MS may depend on the early exposure of the persons with genetic predisposition to an environmental trigger. Nowadays, the environmental factors with the most scientific data are the following: the Epstein-Barr virus, the lack of D vitamin and the tobacco. The genetic studies show the involvement of a major histocompatibility complex class II gene. It's about the HLA-DR2 haplotype DRB1*1501-DQB1*0602. Probably, much more genes contribute cumulatively to the MS risk, and the genes and alleles involved differ from one patient to another.

The pathogenic mechanism of the disease is complex and multifactorial. The T CD4+ lymphocytes play the main role in pathogenesis. The oligodendrocyte is the main target of the immune attack in MS. The myelin proteins are considered to be involved in initiating the immune process in MS. Thus, there are incriminated certain peptide myelin antigens: MOG (myelin oligodendrocyte glycoprotein), MBP (myelin basic protein), PLP (proteolipid protein), α B crystalline, as well as lipid antigens (galactocerebroside, phosphatidylcholine). The antigen is initially displayed outside the central nervous system (CNS) by the antigen presenting cell which belongs to the monocyte line (macrophage, microglia, endothelial cell, astrocyte), towards the T CD4+ lymphocyte. Once the contact with the antigen is made, the T lymphocytes will get involved in the differentiation phase, when a choice is made between the TH1 pathway (pro-inflammatory) which induces the production of the inflammatory cytokines, and TH2 pathway

(anti-inflammatory) which induces the production of the anti-inflammatory cytokines. The toxic inflammatory mediators are released, leading to the breakdown of the blood-brain barrier and to the lesion of the axon and glial cells. The undifferentiated oligodendrocyte precursors act as a source cells whose potential is to remyelinate the demyelinated axons. Over the time, there appears a gliosis which causes a physical barrier for a future remyelination and determines the transition towards a phase with persistent deficit.

The histopathological studies on MS indicate the fact that the demyelinating lesions can be found both in the white matter and in the grey matter (the cerebral cortex and cerebellar cortex). The most common demyelinating lesions are the subpial lesions.

The clinical manifestations are variable, depending on the dissemination of the demyelinating plaques. Thus, there are affected the main myelinating pathways of the CNS: motor, sensitive, cerebellar and optic. At its onset, the most common symptoms are sensitive, ocular and motor. On the other hand, the less common symptoms at its onset are the sexual and sphincter dysfunction, and these symptoms can lead to complications such as infections of the urinary tract, loss of muscle tone, reduction of bone density, as well as to social and psychological complications. The increased body temperature and the physical effort determine the occurrence or worsening of some neurological symptoms or signs (the Uthoff phenomenon) in some patients.

According to the classification made by Lublin and Reingold (1996), there are four types of disease depending on its evolution:

- relapsing-remitting (RRMS)
- secondary progressive (SPMS)
- primary progressive (PPMS)
- progressive relapsing (PRMS)

The most common type is the relapsing remitting form which affects 70-80% of the patients with MS. This subtype is characterized by relapses, followed by partial or complete recovery (remission). The first relapse, considered to be the first neurological episode, is called clinically isolated syndrome (CIS). It can be monofocal or multifocal.

The SP form appears after an average period of approximately 10 years of RR form evolution and is characterized by continuous progression, interrupted sometimes by relapses or

occasional plateaus. The PPMS appears in 10-15% of the patients with MS. In the case of these patients, onset of the disease is characterized by a continuous progression without relapses or remissions.

There are also described a benign variant and a malignant variant as particular forms of MS. Neuromyelitis optica (NMO, Devic's diseases) is considered a variant of multiple sclerosis but it now represents a distinct entity.

At the present time, there is no specific investigation to allow the diagnosis of MS. The diagnostic criteria consist in an ensemble of clinical and paraclinical elements which prove dissemination in time and in space of this disease, after a rigorous differential diagnosis. At present, 2010 revised McDonald criteria, allow a diagnosis of MS after evidence of inflammatory lesions dissemination in time and in space.

The conventional MRI plays the main role in diagnosing and monitoring the activity of this disease as well as in the therapeutic efficiency. This thing explains the necessity of a reproducible and standardized acquisition protocol to standardize the practices and adapt the acquisition techniques to the physiopathology of this disease. In the T_2 weighted sequences or FLAIR, the plaques appear in the shape of hypersignal areas. A variable number (10-20%) of lesions appearing as hyperintense on T_2 weighted, are visible in the form of hyposignal in T_1 weighted sequences. The intravenous injection of the paramagnetic contrast agent (gadolinium), followed by the acquisition of the T_1 weighted conventional sequence allows the detection of the area of blood-brain barrier breakdown secondary to the inflammation, and thus, we can visualize the active lesions. The black holes are considered to be lesions in hyposignal on T_1 highlighted after contrast administration.

After determining the diagnosis of clinically defined multiple sclerosis, it is compulsory to assess the disability level of the patient with the help of the EDSS scale (Kurtzke Expanded Disability Status Scale). Although the EDSS has many limitations as a clinical measure of the disease progression, it represents however the reference tool and no other alternative has proved superiority and simplicity than it so far.

The composite score or the Multiple Sclerosis Functional Composite (MSFC) is another scale which quantifies the disability in the case of multiple sclerosis. It seems to be a complementary method in assessing the invalidity of the upper limbs and cognitive function.

The onset age of the progressive phase is decisive for the long-term prognosis. Other factors of bad prognosis are the male sex, predominance of cognitive, cerebellar and pyramidal symptoms, as well as the MRI aspect: the persistence of the active lesions, extension of lesions with a hypersignal on T_2, T_1 lesion load, atrophy and rapidity of MRI progression.

The necessity of a better understanding of the pathophysiology process implied in the onset of the disease, led to the development of some new conventional MRI techniques. These techniques have the advantage to explore both the white matter and the grey matter, which seem apparently normal, as well as to specify the focal, regional and global tissue lesion. The exploration of the white matter fiber tracts helps to understand the mechanisms of cerebral plasticity.

The analysis of the cerebrospinal fluid (CSF) is a complementary examination necessary in determining the diagnosis of MS, but it is not mandatory in all cases according to the new revised criteria. The presence of the oligoclonal IgG bands (due to an intrathecal synthesis in the CSF), absent in the serum, has a sensibility of 95% and a specificity of 90%.

MS is a diagnosis of exclusion. Numerous and various affections can lead to confusions with MS. From imagistic point of view, there are diseases or structural anomalies which, due to the modifications they present at MRI, can be confused with MS: small vessels disease (cerebral lacunar state, Binswanger's disease), progressive multifocal leukoencephalopathy (PML), leukodystrophies and most of the inflammatory diseases, vasculitis of the central nervous system, CADASIL, migraine, periventricular leukomalacia.

CHAPTER 2. DISEASE-MODIFYING THERAPY

There is no etiologic treatment to determine the healing of this disease.

The therapeutic possibilities can be grouped into three categories: treatment of acute relapse, disease-modifying therapy (immunomodulators, monoclonal antibodies, immunosuppressants) and rehabilitation and symptom management.

The relapse treatment is made with corticosteroids by administering high doses of 1g/day (intravenously 1-2 hours) for 3-5 consecutive days. The efficiency of the corticosteroids is quite

short. The treatment can sometimes extends 5-7 days in case of the severe relapses or of the relapses that cannot be recovered.

The immunomodulating treatment is a first line treatment validated in clinically definite MS, RR and SP types, and in the clinically isolated syndrome (only certain drugs are indicated for the SP forms).

Glatiramer acetate (Copaxone) is approved in Europe for RRMS, and for clinically isolated syndrome (CIS), and should be taken subcutaneously in daily doses of 20 mg. As there is no potential risk of depression, the glatiramer acetate can be used in patients with depression. Apart from the interferon beta, the treatment with Copaxone cannot be associated with the cytolytic hepatitis, hematologic disorders and neutralizing antibodies.

At the present time, there are approved four preparations of interferon beta (IFN beta). Interferon beta-1a (Avonex) is recommended in relapsing-remitting MS and in CIS; it is administered intramuscularly in doses of 30 µg (6 million UI), once a week. Interferon beta-1a (Rebif) is indicated in the case of relapsing-remitting MS and in CIS; it is administered subcutaneously in doses of 44 µg three times a week (it is recommended to begin the treatment with doses of 22 µg, subcutaneously, three times a week, in the first month, in order to reduce the risk of side effects). Interferon beta-1b (Betaferon and Extavia) is indicated in relapsing-remitting MS and in CIS; it is administered subcutaneously in doses of 25 (8 million UI) once in two days. Neither glatiramer acetate nor one of interferon beta forms are approved to be used by the women who are pregnant or who give suck to a child.

The studies which compare IFN beta with glatiramer acetate have proved there is no difference concerning the clinical efficiency between the two preparations. There is a mutual consensus according to which the immunomodulating treatment should be initiated as soon as possible after having established the diagnosis of certitude for the RRMS and in the patients with CIS which run the high risk to be then diagnosed with the clinically definite MS. Once initiated, the therapy has to be continued for an indefinite long time, and the patients have to be carefully monitored in order to maintain a good compliance with the treatment.

Various trials which studied IFN beta-1a and IFN beta-1b suggest that the patients with SPMS, with an inflammatory acute component, can benefit from the treatment with one of the interferons. Interferon beta doesn’t have any indication in the primary progressive forms.

The neutralizing antibodies appear frequently when using interferon beta-1b, but in the course of time, the level of the serum titre lowers significantly while the treatment continues without being changed. The neutralizing antibodies interfere with the pharmacodynamic, clinical effects as well as with the MRI ones.

Natalizumab (Tysabri) is a humanized monoclonal antibody against the α4 integrin which is approved in MS treatment from 2006. Its efficiency seems better than the treatment with interferon and glatiramer acetate. Under the form of monthly intravenous perfusion of 300 mg, Natalizumab is indicated as monotherapy for the treatment of the patients with very active relapsing-remitting MS (objectified by cerebral MRI), despite the immunomodulatory treatment, or for the patients who show severe relapsing-remitting MS, with 2 or more relapses which cause disability in the course of one year. In general, natalizumab is well tolerated. Rarely can occur deceases as a result of the development of a progressive multifocal leukoencephalopathy (PML).

The immunosuppressive treatment is indicated in SPMS, or in the case of failure of the immunoimodulatory treatment.

Approved by the FDA in 2000, mitoxantrone is a chemotherapic agent used to treat secondary progressive MS and very active relapsing-remitting MS. Mitoxantrone is approved in doses of 12 mg/m² of body surface, administered intravenously once in 3 months, with a maximum dose of 140 mg/m². The most important side effects are the cardiologic and hematologic ones.

Azathioprine is used as a second line drug in doses of 100-200 mg/day without influencing significantly the progression of the disease.

Methotrexate is administered orally in doses between 7,5-20 mg once a week. In the improvement of the disability and MRI lesions, its results are quite modest.

Cyclophosphamide is used in the treatment of progressive MS with active disease. It is administered in perfusion at an iv dose of 600 mg/m², once a month, with a maximum cumulative dose of 20 grams.

Mycophenolate mofetil has been recently proposed in the treatment of primary progressive MS or of secondary progressive MS.

Figolimod (FTY 720), a modulator of the sphingosine 1-phosphate receptor, is the first drug with oral administration approved in the United States and Europe for relapsing remitting

MS. Its efficacy is demonstrated both on clinical and radiological parameters, compared to a reference treatment in relapsing-remitting MS. It is recommended a daily dose of 0,5 mg. The tolerance is generally a good one.

Cladribine is another drug with oral administration indicated in patients with relapsing-remitting MS. The phase III Clarity study proved the superiority of cladribine versus placebo. But this drug is not approved in the United States and Europe.

Laquinimod is an immunomodulator which belongs to the linomide family, which is studied for the treatment of MS. Two phase III studies (ALLEGRO and BRAVO) show a significant reduction of the rate of relapses and of the disability progression in comparison with placebo. They also show the fact that laquinimod has a very good safety and tolerability profile.

Teriflunomida, the active metabolite of leflunomide, an immunosuppressive drug used in the treatment of rheumatoid polyarthritis, was evaluated in a phase III study (TEMSO) as a medication for MS. At MRI, the results of this study show a significant reduction of the active lesions (as well as of total lesion load), of the number of relapses per year compared to placebo, and of the disability progression.

BG-12 is the oral version of dimethyl fumarate. Two phase III studies (DEFINE and CONFIRM) with dimethyl fumarate in patients with relapsing-remitting MS made evident a significant reduction of this disease activity at MRI and of the disability progression, compared to placebo or glatiramer acetate.

Nowadays, many monoclonal antibodies are the subject of MS studies and there should be inaugurated a second generation of natalizumab: alemtuzumab, daclizumab, ocrelizumab.

The drugs with potential neuroprotective effect are: the glutamate receptor antagonists, minocycline, erythropoietin, lamotrigine and phenytoin.

In the case of children, the recommendations of the therapeutic approach in MS, approved by mutual consent, are the following: methylprednisolone iv as the first line treatment for acute relapse, IFN–β and glatiramer acetate as the first-line disease-modifying therapies.

The most common symptoms, which can interfere with the daily activities and the quality of life, met in patients with multiple sclerosis, are the following: the reduction of mobility, chronic fatigue, balance disorders, sphincter and bowel dysfunction, spasticity, pain, cognitive disorders, depression, tremor, sexual dysfunctions and paroxysmal phenomena. The

identification and treatment of all those symptoms represent an important aspect of the MS management.

The rehabilitation and symptom management has as objectives: to reduce disability, prevent the complications of the disease and increase the quality of life. The physical therapy can improve or maintain the core stability and motility. It can also prevent contractures. By combining the physical therapy with the occupational therapy, it helps to improve their quality of life and maintain their social integration as much as possible.

4-aminopyridine is a drug approved by the FDA in January 2010 and is indicated for the improvement of walking in adult patients with MS with walking disability (EDSS 4-7). It acts as a potassium channel blocker. It is administered in doses of 10 mg every 12 hours and can be used simultaneously with the disease modifying therapy.

The various studies done so far have shown MS doesn't affect fertility, doesn't increase the risk of malformations or complications during pregnancy or childbirth. The frequency of relapses diminishes during pregnancy, but during the first postpartum 3-6 months, their frequency increases. The women who undergo a treatment with IFN-beta or glatiramer acetate have to interrupt the treatment one month before getting pregnant, while the women who undergo the treatment with natalizumab or immunosuppressive therapy will have to interrupt it 3 months before getting pregnant. The disease modifying therapy has to start as soon as possible after childbirth in the case of the women with previously diagnosed active disease.

CHAPTER 3. COPING STRATEGIES

The word "coping" derives from English, "to cope with", and it means "to deal with, to adapt to". The word coping is defined as representing the efforts for managing the environmental requirements and intrapsychic conflicts, which exceed or not the resources of a person.

In 1966, Lazarus introduced the notion of coping in the psychological parlance. Later, this was taken over by authors interested in stress problems. Nowadays, it is one of the most common notions used in the specialty literature.

Coping is the way in which people act when they are in a front of a situation that they perceived as being difficult, in order to pass over it, to control it. Thus, coping supposes a prevention mechanism and stress adaptation resulting in reduction of the stress intensity.

In the specialty literature, because coping is characterized by adaptation and prevention mechanisms, some distinct approaches were outlined: the medico-biological approach, psychoanalytic theory and cognitive theory.

The main cognitive defensive constructs are: defensive denial (refusal), repression, projection, rationalization, intellectualization/isolation.

Coping includes all the ways of managing the stress and can be approached as being both an adaptive or disadaptive mechanism of adaptation to stress.

The classical classification splits coping into two main functions: the problem-focused coping (it includes strategies addressed directly to the problem, strategies of acceptance concerning the confrontation with the stressor agent) and emotion-focused coping (it includes strategies which aim at adjusting the emotions associated to the problem; due to it, a decisive confrontation with the stressor agent is postponed or it even doesn't take place anymore).

The emotion-focused coping is also called the passive/avoidant coping. In order to control the emotional tension, people use strategies focused on emotion: avoidance, positive re-evaluation, self-blame, threat minimization, expression of emotions (by attack of cry or fit of anger), expectation of a miracle.

The unpredictable nature of a disease can play an important part in the coping strategy that is used. In this case, the emotion-focused coping is frequently used.

In the specialty literature it is known the fact that the "problem" strategies are the most efficient strategies in decreasing depression and anxiety. They are correlated with a better quality of life. On the other side, the "emotion" strategies are associated with a deterioration of the quality of life.

Multiple sclerosis is an invalidant disease affecting especially young adults. It has an unpredictable evolution towards major disability in a variable period of time. This progressive unpredictability has a psychological and physical impact on the life of these persons who are in that period when they have family and socio-professional projects. Thus, during the disease evolution, the patients with MS will develop different coping strategies in order to be able to

adapt themselves to the complications of the disease. Various factors influence the coping strategies and the quality of life of the patients with MS. As a result, the coping is different from one person to another and can change over time depending on the situation.

In MS, the emotion-focused strategies are directed towards the reduction of the emotional distress caused by the stressing situation, while the problem-focused strategies are directed towards modifying the stress sources. By using a problem-focused coping, the quality of life can be improved.

The study of the coping strategies allows us to understand better the difficulties that the patients with MS have to deal with, the patient's ways and abilities of adaptation both when they are informed that they suffer from MS and during the evolution of the disease. Thus, we can also find better therapeutic methods. Depending on the coping strategy that is used, on the quality of the social support, the neurologist can evaluate the level of information that is going to be given to the patient as well as the acceptance of the proposed treatment.

CHAPTER 4. EXPERIMENTAL INVESTIGATIONS AND INTERVENTION STRATEGIES CONCERNING PATIENTS WITH MULTIPLE SCLEROSIS

AIM OF RESEARCH

Assessment of disability and pointing out of clinical and imaging correlations with the purpose of improving the medical act. Identification of the coping strategies used in patients with multiple sclerosis (MS) in order to draw up a intervention and health care plan.

GENERAL HYPOTHESIS

The patients with clinically definite MS with disease-modifying treatment show a reduction of disability progression rate and a reduction of the progression rate of the lesion load (measured imagistically with magnetic resonance) during the disease evolution, compared to the untreated patients with MS.

WORKING HYPOTHESES

I1. The level of the cerebral lesion load in patients with MS correlates positively with the level of physical disability.

I2. The diagnosis of clinically definite MS and the disease evolution determine the development of some coping strategies.

RESEARCH OBJECTIVES

O1. To establish the diagnosis of certitude in patients with multiple sclerosis;

O2. To assess the level of physical disability by using the specific tools;

O3. To measure quantitatively the cerebral lesion load in patients with multiple sclerosis;

O4. To establish the correlation between the cerebral lesion load, age, disease duration and the level of the physical disability in patients with multiple sclerosis;

O5. To explore the relationship between the clinically definite MS and coping strategies.

The research was undertaken in Clinic of Neurology of Academic Emergency Hospital Sibiu during November 2008 – October 2012. This research has a quantitative design. The research theme was studied within the context of an observational study. The approach is a prospective and retrospective longitudinal one.

There were formed two groups necessary for the development of this research: the group of patients (made up of 61 patients with the diagnosis of clinically definite multiple sclerosis) and the control group (made up of 61 healthy patients recruited consecutively, and whose sex, age and level of study correspond to the group of patients). Out of the 61 patients with MS, included in the study, a number of 37 patients agreed to be assessed from psychological point of view.

With a view to testing the hypothesis and to achieving the proposed objectives, we used the following methods: the observation, magnetic resonance imaging, scales to assess the moticity, scales to assess the coping strategies, experiment.

The observation method consists in monitoring intentionally and systematically the specific phenomena, without any intervention from the part of the researcher, with the purpose of explaining, understanding and improving them.

Magnetic resonance imaging is a non-invasive technique of medical imaging which allows us to visualize the organs and tissues with a great accuracy.

All the patients with MS were imagistically examined, according to the same MRI protocol, by using a Siemens 1.5 T MRI scanner. The processing of the images was realized in

collaboration with the Biological and Medical Magnetic Resonance Center - Faculty of Medicine of Marseille (Centre de Résonance Magnétique Biologique et Médicale - Faculté de Médecine de Marseille). The cerebral lesion load was calculated by using a semi-automatic and reproducible technique, a technique which outlines the lesions after segmenting the images (Java Image, Version 3.0; Xinapse Systems, Leicester, England).

After the acquisition of images, in order to identify and quantify the volume of cerebral lesions, we went through the following phases: image pre-processing, image segmentation, identification of lesions with T_2 hypersignal and of lesions with T_1 hyposignal.

The motor assessment scales used in the study were the EDSS **(**Expanded Disability Status Scale) and MSFC **(**Multiple Sclerosis Functional Composite).

The coping strategies were assessed used the SACS scale (Strategic Apporach to Coping Scale), a strategic and faithful tool of assessment developed by Hobfoll and his collaborators in 1993 and based on the multiaxial model of coping.

The development of a medical experiment implies many more phases: the pre-experimental phase, the experimental phase, the post-experimental (posttest) phase and the retest phase. The results obtained in the medical experiment are considered to be statistically significant or insignificant depending on comparisons made between the intra-group (in the case of the unique samples) or intergroup (in the case of the parallel samples).

The processing and analysis of the data obtained in this study were realised by using the SPSS statistical software, version 17.

CHAPTER 5. DATA ANALYSIS AND INTERPRETATION

In this study, there were included 61 patients with multiple sclerosis. Depending on the type of disease, they were divided in the following way: 47 patients with relapsing-remitting multiple sclerosis (RR-MS), 10 patients with secondary progressive multiple sclerosis (SP-MS) and 4 patients with primary progressive multiple sclerosis (PP-MS). The data analysis and interpretation were done depending on the type of disease.

In the case of the patients with relapsing-remitting multiple sclerosis, both at baseline and at end of the study, there was obtained a statistically significant correlation between the disability

score provided by the EDSS scale and the age, disease duration, average volume of T_1 and T_2 lesions. The EDSS score correlates significantly statistically with the motor disability tests for the upper limbs (9HPT) and for the lower limbs (T25-FW). Both at baseline and at the end of the study, in the case of the patients who follow the treatment with IFN, there is noticed a statistically significant difference in comparison with those patients who don't follow the disease-modifying treatment concerning the disability level and the average volume of the cerebral lesions. There is also noticed a statistically significant progression of the average values after 4 years in the case of the following parameters: EDSS, 9HPT, T25-FW and average volume of the T_2 lesions.

Concerning the average values of the T1 lesion volume, there is noticed a statistically insignificant progression after 4 years (p=0,119). The tendency of stabilizing the T_1 lesion average volume can be explained by the fact that the treatment with interferon has a beneficial effect because it reduces the accumulation of "black holes", an effect which is proved by many studies.

In progressive MS, the average age when the progression begins, is similar. Those patients are elder then those with RRMS and they have a similar clinical progression.

The patients with progressive MS have a lesion load bigger in comparison with those with RRMS.

In the case of the patients with progressive MS, between EDSS score and the average volume of T_1 and T_2 lesions, both at baseline and at end of the study, there were obtained statistically insignificant correlations between those parameters. This thing can be explained by the fact that the lesions disposition in certain anatomical areas of brain can be held responsible for the aggravation of disability, while a part of the lesions is "clinically silent". On the other side, EDSS score correlates significantly statistically with the motor disability tests: 9HPT and T25-FW.

At the end of the monitoring period, in the case of the patients with progressive MS, there is noticed statistically significant aggravation of the physical disability assessed by EDSS score and motor disability tests: 9HPT and T25-FW. In addition to it, there is emphasized a statistically significant increase of the average volume of the T_1 and T_2 lesions.

CHAPTER 6. COPING STRATEGIES IN MULTIPLE SCLEROSIS

After analyzing the distribution of the types of coping strategies used in the patients assessed in this study, it is noticed that the most common used coping strategy is avoidance, followed by strategies such as indirect action, instinctive action, seeking social support and aggressive action.

There were emphasized strong correlations between the following coping strategies: aggressive action and antisocial action, indirect action and antisocial action, cautious action and avoidance, indirect action and aggressive action.

From this correlational analysis, there can be noticed the fact that between the assertive action and aggressive action, there is a level of significance with p=0,004. A p=0,005 is represented by the relationship between the strategies of social relations and the social support as well as of social relations and avoidance.

By analysing the significant correlations, it was tried to identify the predictor variables (independent), those variables which act on other variables (dependent) and which don't correlate between them. This analysis was done in order to realize a multiple linear regression with a view to emphasizing and estimating the values of a variable in relation to the other one, as well as to explaining relationship between them. Therefore, the predictor variables highlighted by these correlations, are represented by the following strategies: cautious action, social relations and social support, while the dependent variable is the avoidance strategy.

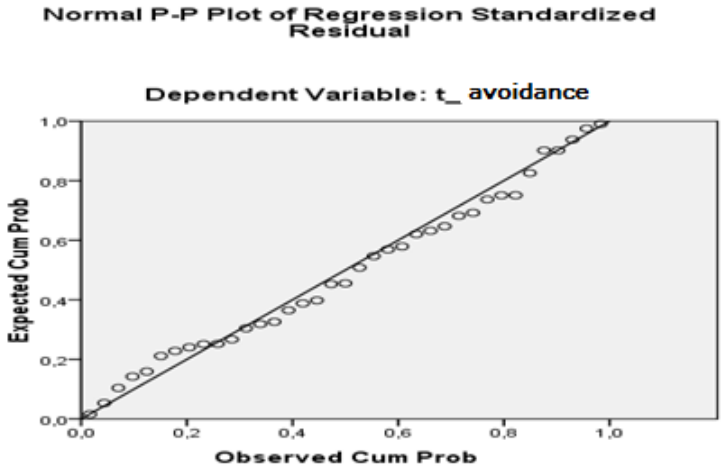
With these results in view, we state that there can be made a prediction on these variables by using the multiple linear regression. In the equation there are included all the predictor variables, and the effect of each variable is assessed after and independently of the effect of the other variables.

There is noticed a statistically significant correlation between the following variables: avoidance-cautious action (p=0,001) and avoidance-social relations (p=0,002). The independent variables (cautious action and social relations) do not present statistically significant correlation (p=0,250), thing that allows us make a prediction on the dependent variable (avoidance).

In the case of the model with predictor variables (cautious action and social relations), the level of significance has a p<0,05 representing the statistically significant coefficients. The social

support variable was excluded after analyzing the Beta coefficients because it didn't meet the criteria of inclusion in the regression model.

The mean of the residual values is zero, the standard errors do not correlate with the predictor variables and show a normal distribution; this means that the errors of prediction comply with the main conditions for the model of multiple linear regression. The normal distribution of the standardized cumulative residual values is rendered in the below chart which shows us a good level of superposition over the theoretical model (the straight line) and the fact the requirement concerning the normality of residual values was met.



The results obtained in this study show us that most of the patients with multiple sclerosis use an emotion-focused coping model.

CHAPTER 7. DISCUSSION AND CONCLUSIONS

The results of this research emphasizes a statistically significant correlation between disability and age, disease duration, cerebral lesion volume both at baseline and at end of it, in the case of patients with RRSM. Concerning the disability level and the average volume of the cerebral lesions, there is also noticed a statistically significant difference between the patients who follow the treatment with IFN and the patients who do not follow the modifying-disease treatment. Thus, there is noted that the beneficial effect of the immunomodulating treatment

when stabilizing the disability progression and the cerebral lesion load during the disease evolution. When we correlate the disability with the volume of the cerebral lesions, we have to have in view the limits of the EDSS scale: the intra/inter-observer variability and the rate of EDSS progression which is not constant over time.

In the case of the progressive MS, between the EDSS score and the average volume of the T_1 and T_2 lesions, there was obtained a statistically significant correlation at baseline at end of the study, there are noticed statistically insignificant correlations between the same parameters. This lack of correlation can be explained by the fact that the lesions disposition in certain anatomic areas of the brain can be held responsible for the aggravation of disability while a part of the lesion is "clinically silent". Thus, there was developed the "clinico-radiological paradox" concept, determined by various limits of the conventional MRI to detect the pathological aspects and the compensatory skills of the cerebral tissue. On the other side, the T_1 lesion volume correlates with the volume of the destroyed cerebral tissue, and is considerably lower than the T_2 lesion volume. Thus, the T1 lesion load is lower in the given areas compared to T_2 lesion load, thing that reduces the possibility of correlation with the clinical results.

Both in the group of patients with RRSM and in the group of patients with progressive SM, the EDSS score correlates statistically significantly with the tests of motor disability for the upper limbs (9HPT) and for the lower limbs (T25-FW). The studies show a very good intra/inter-observer reliability of the MSFC, which is more sensitive to changes than EDSS.

At end of the period of study, both in the case of the patients with RRSM and in the case of those with progressive SM, there is noticed a statistically significant progression of the average values for the following parameters: EDSS, 9HPT, T25-FW and the average volume of the T_2 lesions.

We have to take into account the reduced specificity of the lesions with hypersignal on T_2 due to the heterogeneous pathological substrate: edema, inflammation, demyelination, gliosis and axonal loss. Thus, the MRI is the routine investigation in monitoring the MS progression, but is not sufficient to be used as a predictor of disability.

We can draw the conclusion that the assessment of the disease progression and of the response to treatment, brings about many more limitations concerning: the variable duration of the disease at the inclusion in the study; the variable duration from the first symptom until the

moment when the treatment begins; the duration of the disease modifying treatment (there are patients with RRSM, with a long duration of disease, who do not follow any treatment); the variable rhythm of the disease progression (the rate of EDSS progression is not constant over time); the number of patients included in the study and the inclusion criteria (the patients selected according to very restrictive criteria are not representative for the general population).

The unpredictable character of the MS evolution influences the way in which the patients with multiple sclerosis adapt to the emotional distress. The aim of this research is to understand better the difficulties that the patients with MS have to deal with and to find more adequate therapeutic methods.

The analysis of the statistical data shows the fact that the best regression model is represented by the model of the following predictors: cautious action and social relations. This thing determines the exclusion of the social support model from the final equation (it does not meet the inclusion criteria in the regression model).

After analyzing the matrix of intercorrelations between the independent variables, it was proved the absence of a statistically significant correlation. This thing was also proved by the collinearity model.

Therefore, we can conclude that, following the results obtained in this study, most of the patients with multiple sclerosis resort to the emotion-focused coping more frequently than to an adaptation focused on problem-solving.

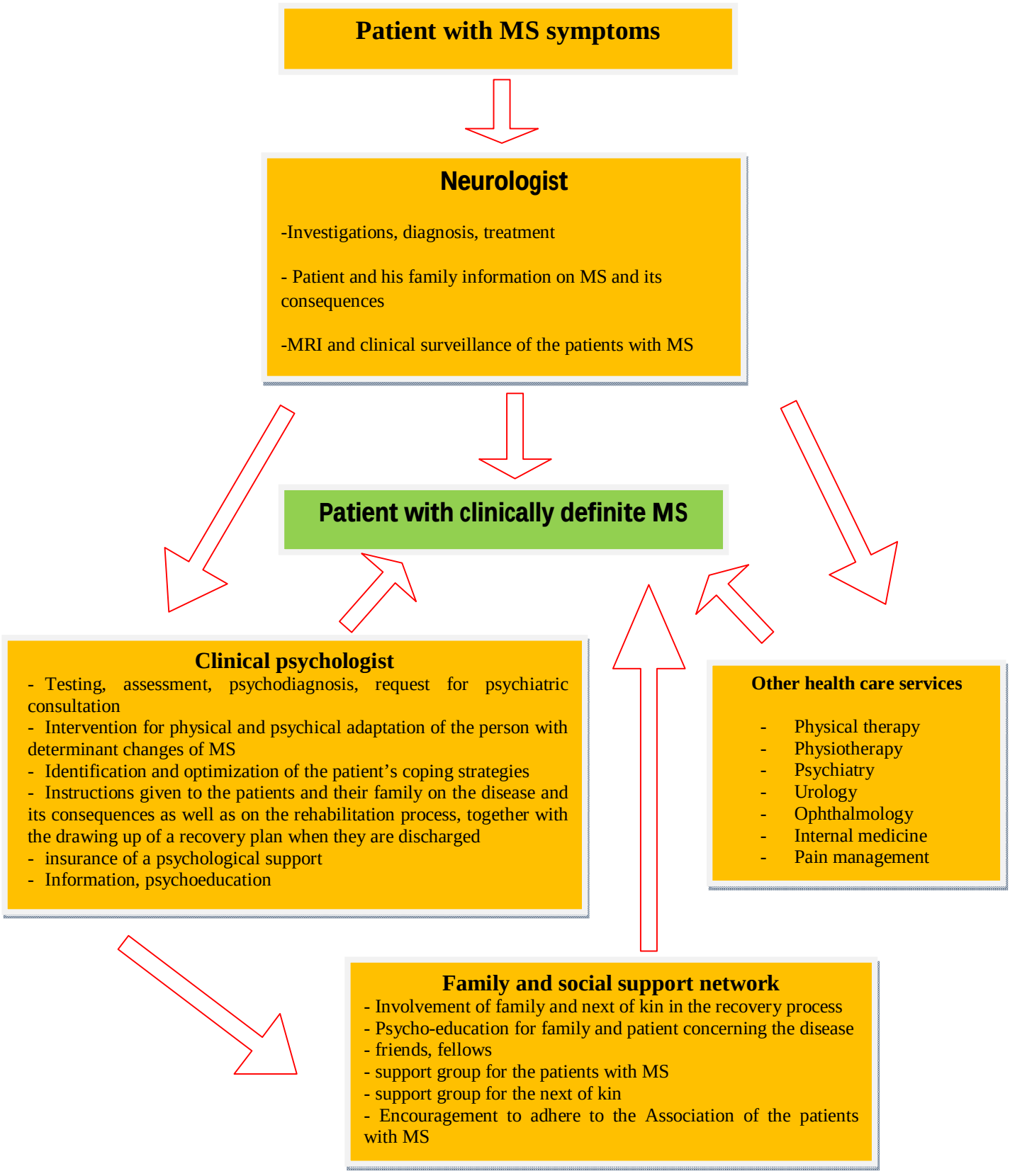
CHAPTER 8. HEALTH CARE AND INTERVENTION PLAN FOR PATIENTS WITH MULTIPLE SCLEROSIS

The analysis and interpretation of the results obtained in the present study, allowed us to elaborate a treatment and diagnostic algorithm of the patients with MS which includes short and long term objectives.

Taking into account the considerable impact that this pathology has on the quality of a patient’s life, we emphasize the necessity of forming a multi-disciplinary team who should intervene in the management of the various disorders.

Thus, we propose an algorithm which can represent a useful working tool in all the basic health services, starting with the family physician and ending with the neurologist, psychologist, psychotherapist, all those who intervene in the management of the patients with MS in one way or another.

ALGORITHM


Patient with MS symptoms
Neurologist
-Investigations, diagnosis, treatment
- Patient and his family information on MS and its consequences
-MRI and clinical surveillance of the patients with MS
Patient with clinically definite MS
Clinical psychologist
- Testing, assessment, psychodiagnosis, request for psychiatric consultation
- Intervention for physical and psychical adaptation of the person with determinant changes of MS
- Identification and optimization of the patient's coping strategies
- Instructions given to the patients and their family on the disease and its consequences as well as on the rehabilitation process, together with the drawing up of a recovery plan when they are discharged
- insurance of a psychological support
- Information, psychoeducation
Other health care services
- Physical therapy
- Physiotherapy
- Psychiatry
- Urology
- Ophthalmology
- Internal medicine
- Pain management
Family and social support network
- Involvement of family and next of kin in the recovery process
- Psycho-education for family and patient concerning the disease
- friends, fellows
- support group for the patients with MS
- support group for the next of kin
- Encouragement to adhere to the Association of the patients with MS

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