COMORBIDITIES AND SIDE EFFECTS OF THE IMUNOMODULATORY TREATMENT IN MULTIPLE SCLEROSIS

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Summary

Multiple sclerosis is a demyelinating, neurodegenerative disease of the central nervous system, that affects the young adult and is associated with a high degree of disability. Physical and mental comorbidity and adverse health behaviors are common in patients with MS. Comorbidities and health behaviors are associated with adverse outcomes in MS and should be considered in the assessment and management of patients with MS.

We have studied a group of 150 MS patients treated with immunomodulators inside the Romanian national MS treatment programme. The patients we analysed corresponded to the available literature in matters or number, age and sex. We searched for associated pathology and side effects of the treatment. After selecting and statistically analyzing the data we concluded that dyslipidemia was the most common comorbidity, followed by hyperglicemia and vertebral hernia. The presence or not of a comorbidity before the treatment does not relate to the EDSS score ($p<0.05$). Thus the presence or not of an associated pathology during 7 years of immunomodulatory treatment does not affect the patient's EDSS score and disability. The most frequent side effects in our study were anemia, thrombocytopenia, raised liver enzymes, dyslipidemia, lymphocitopenia and neurtropenia. The anemia was a mild one, with no significantly decrease haemoglobin and hematocrit levels. The same is observed with the liver enzymes, while the increase in SGOT and SGPT values are 40% increase in comparison with the maximum accepted normal value. Summarizing the results of the side effects, it seems that as time of treatment rises, the side effects free patients decrease in actual number.

Key words: multiple sclerosis, comorbidities, side effects

Introduction

Multiple sclerosis is a chronic, inflammatory demyelinating, neurodegenerative disease of the central nervous system, characterised by the destruction of myelin sheathsof the nerve fibers with a relative sparing of the axons, the infiltration of inflammatory cells in a perivascular and paravenous distribution and the formation of plaques manily in the white matter in specific places. This neurological pathology affects 2,5 million young adults worldwide and in the USA 200 new patients are diagnosed with MS every week, according to the national MS society. In Romania, the incidence raised in the last years and because it is a disabilitating disease among the young population (20^{th} and 30^{th} decade) there are many studies involving MS. Besides the pathology and the disability that MS has, these patients come with other diseases and comorbidities, quite frequent also [1].

In a study conducted in France by Fromont et al, published in 2013, among 22,087 patients, 653 (3%) had a comorbidity status diagnosed at the same time as MS. Of these comorbidities, 86.8% could be grouped into five main categories: psychiatric disease (40.2%), autoimmune disease (24.5%), cardiovascular disease (16.2%), cancer (12.2%), and metabolic disease (9.0%). Psychiatric disorders and diabetes were more frequent in MS patients than in the general population of the same age [2]. Canadian scientist Marrie and Hanwell researched the general health issues in MS and concluded that mental comorbidity is common in MS; depression has a lifetime prevalence of 50%, while anxiety has a lifetime prevalence of 36%. Physical comorbidity is also common, with the most frequently reported conditions including hyperlipidemia, hypertension, arthritis, irritable bowel syndrome, and chronic lung disease. Fracture risk is increased among patients with MS because of an increased risk of osteoporosis and propensity for falls. Vitamin D insufficiency is common and may contribute to increased fracture risk and increased disease activity. Comorbidities and smoking are associated with diagnostic delays, increased disability progression, lower health-related quality of life, and lower adherence to treatment [3].

There are many theories about the ethiology of MS but none proved to be the certain one. Thus the treatment for MS is not one curative, but instead trying to modulate the immune response. According to major populational studies so far the immunomodulatory treatment proved to modify the natural evolution of this disease, by lowering the relapse rate and the disability after a relapse, prolonging in this way the handicap free duration and quality of life for MS patients. But, this treatment comes with side effects, mostly manageable [4].

The immunomodulatory treatment for MS is composed by interferons, glatiramer acetate and natalizumab. The interferons (IFN) are anti-inflammatory cytokines and they are one of the body's earliest responses to a viral infection. Additionally, they present antineoplastic and immunomodulatory activity, by regulation of cell growth and proliferation, and modulation of immune responses [5]. Interferons are classified according to the cell type from which they were initially delivered. The MS therapy uses INF β 1a and 1b under different commercial names. The adverse effects of IFN administration are many. The most frequent one is the flu like syndrome that occurs in 50% of the treated patients. This includes fever, chills, weakness, fatigue, myalgia and arthralgia. The flu like syndrome may follow each injection, but it does not last more than 24 hours and it occurs mainly during the first weeks or months of treatment and after many repeated doses the drug becomes well tolerated. In some few cases, the symptoms persist and the discontinuation of therapy should be considered. Another side effect are the reactions at the injection sites, in 90% of patients, like pain, redness, induration and rarely, skin necrosis. Other side effects include headache, dizziness, agitation, insomnia and anxiety. Depression is common, with rare suicidal behaviour. Myelosupression occurs frequently and

may be dose limited. Gastrointestinal symptoms like nausea, vomiting, diarrhoea and anorexia appear often. Biological side effects include increased liver enzymes, low leucocytes, renal toxicity, proteinuria [6, 7].

Glatiramer acetate is a synthetic mixture of random acetate salts of polypeptides, which are composed of four naturally amino acids L-alanine, L-glutamic acid, L-lysine and L-tyrosine. Practically glatiramer acetate is a myelin basic protein fragment (MBP) and in MS was designed to inhibit the T-cell response to MBP, and also to inhibit the possible autoantigenes and cross-react with MBP. The side effects of glatiramer acetate are minimal and it is generally well tolerated. The primary side effect is the local injection site reactions that occur in 90% of patients. They consist of erythema with or without induration, brief pain, subcutaneous lipoatrophy, but never skin necrosis. Another self-limiting post-injection reaction with flushing, sweating, throat constriction, chest tightness, dyspnea, anxiety and palpitation that last up to 30 minutes are reported in almost 30% patients. Other experienced side effects include vasodilatation, asthenia, infection, pain, nausea, arthralgia and hypertonia [8]. The difference between IFN and glatiramer acetate is that some patients treated with IFN can develop neutralising antibodies to IFN and therefore the drug will not be able to maintain its functions. Also both therapies are considered to be teratogenic and should not be administered during pregnancy [9].

Natalizumab is a monoclonal antibody, an antagonist of the a4 integrin which is expressed on the surface of the inflammatory lymphocytes and monocytes. By binding to this protein, natalizumab increases the circulating pre-B and B-cells, and therefore the CD19+ mature B cells, decreasing in this way the manifestations of disease activity and inflammation [10]. More precisely, it was observed a 66% reduction of relapses, while 76% of patients were relapse free, the MRI lesions decreased by 92% and the number of T2 lesions was reduced by 80% according to the AFFIRM study [11]. Among the adverse effects of natalizumab is the production of antibodies against it. In the AFFIRM trial, antibodies were detected in 8% of patients at the beginning of treatment and in 88% of patients after the first 12 weeks of treatment. Other side effects include headache, nausea, urticaria and low leucocytes count. The most important adverse effect in positive JC virus patients is the developing of the multifocal leukoencephalopathy, which untreated leads to death. The risk of developing this pathology is estimated to be one person from every 1000 patients treated for an average of 17.9 months [12].

Material and method

The main goal for this study was to observe the adverse effects of the immunomodulatory treatment on MS patients, but also to register the associative pathology they presented. The 150 patients included in this study were in the evidence of the Neurology Clinic in the Clinical Rehabilitation Hospital and also treated inside the Romanian National MS Treatment Programme. The criteria that was defined for the selection of patients to enter this study was the following:

- Age between 18 and 60 years old
- Confirmed MS diagnosis
- Relapsing remitting or secondary progressive form of MS
- Agreement from patients that their personal data and the results of this study could be used for further observations and publications.

The method used was clinical examination, together with the detailed medical and family history, EDSS score determination and biological (blood) analyses. The medical history was necessary in order to determine the comorbidities of the patients, the life style and risk factors. The clinical examination was performed to establish the EDSS score and to take blood for the biological analyses. All data were analyzed in SPSS.20 statistical programme.

Results

We have studied 150 patients from the records of the Neurology Clinic inside the Clinical Rehabilitation Hospital Iasi, among which 38 were receiving Avonex (IFN β-1a), 41 patients were treated with Rebif (IFN β-1a), 34 with Copaxone (glatiramer acetate) and 37 with Betaferon (IFN β-1b).

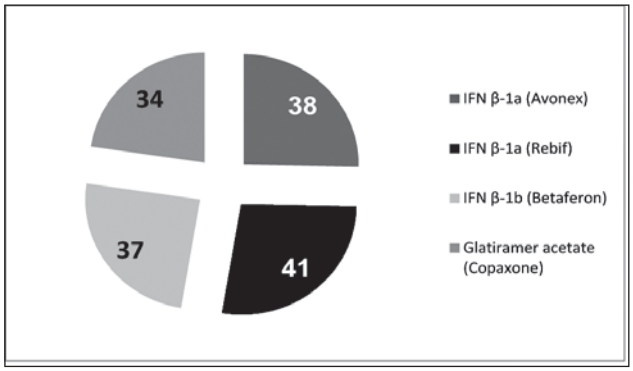

Figure 1. *Distribution of the immunomodulatory treatment*

The associated pathology (comorbidities) was studied in order to observe whether other diseases than MS may influence the treatment outcome or the progression of the disease. The following table consists of the associated pathology that was met in our patients during the years of treatment. It is demonstrated that total sample, the actual frequencies

of the cases and the percentages of every case. As we notice from a total sample of 150 patients only 71 had no associated pathology (47,3%). This means that one out of two patients had an associated pathology. On the other hand the 25,3% of the patients was confirmed to have dyslipidemia and 8,7% hyperglycemia.

Table 1

Distribution of the comorbidities in our study

Comorbidities	Actual frequencies	Percentages
No comorbidities	71	47,3%
Dyslipidemia	38	25,3%
Hyperglycemia	13	8,7%
Vertebral hernia	9	6%
Arachnoid cyst	6	4%
Iron deficiency anemia	6	4%
Hypertension	5	3,3%
Obesity	3	2%
Undefined neoplasia	3	2%
Hepatitis B	3	2%
Thyreoidopathy	2	1,3%
Osteoporosis	2	1,3%
Other (ulcer, osteonecrosis, venous insufficiency, Raynaud syndrome, arythmias, tuberculosis, uterine fibroma, Lyme disease)	15	10%

Considering the tabel above we can conclude that dyslipidemia is the most common comorbidity, followed by hyperglicemia and vertebral hernia. Proceeding with the analysis we will examine if the associated pathology influenced the EDSS score. As we will notice in the following statistical tables the estimated value of the EDSS score before the treatment for those patients with associated pathology is 2.14 and for those with no associated pathology 2.24. The deviation is estimated at 0.09, which is not considered statistically significant. Thus the presence or not of a comorbidity before the treatment does not relate to the EDSS score ($p<0.05$).

Table 2

Group statistics fro EDSS and associative pathology

No associated pathology	N	Mean	Std. deviation	Std. Error Mean
EDSS yes	71	2,1479	.93787	.11130
No	79	2,2405	1,08489	.12206

In the following tables we have examined the influence of associated pathology on the EDSS score after a period of 7 years of immunomodulatory treatment. As we noticed the estimated mean value of the EDSS for those patients with associated pathology is 3.00 and for those with no associated pathology is 2.4. The deviation is estimated at 0.59 which is not considered statistically significant. Thus the presence or not of an associated pathology during 7 years of immunomodulatory treatment does not affect the patient's EDSS score and disability.

Table 3

Group statistics for EDSS at 7 years of treatment and associative pathology

No associated pathology	N	Mean	Std. deviation	Std. Error Mean
EDSS 7y yes	7	3,000	1,32288	.50000
No	11	2,4091	1,48017	.44629

As for the side effects of the immunomodulatory treatment, first we analysed the patients whose period

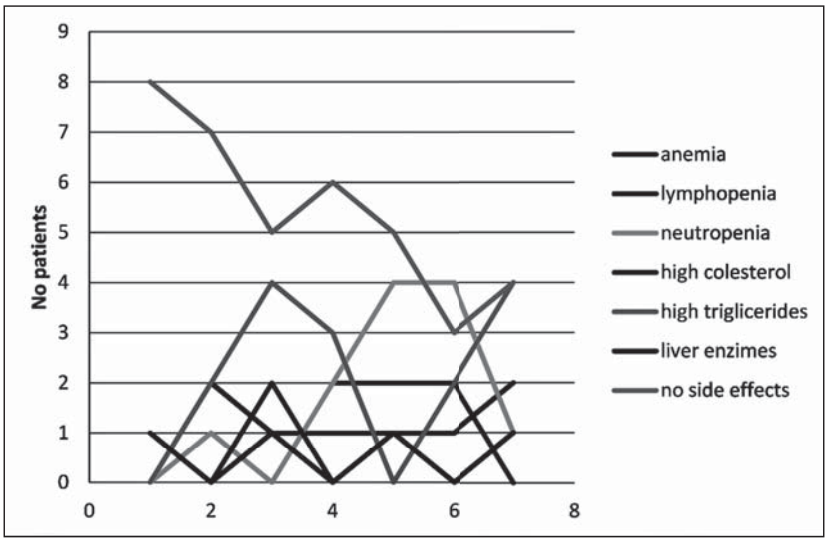

Figure 2. *Side effects of 7 years treated patients.*

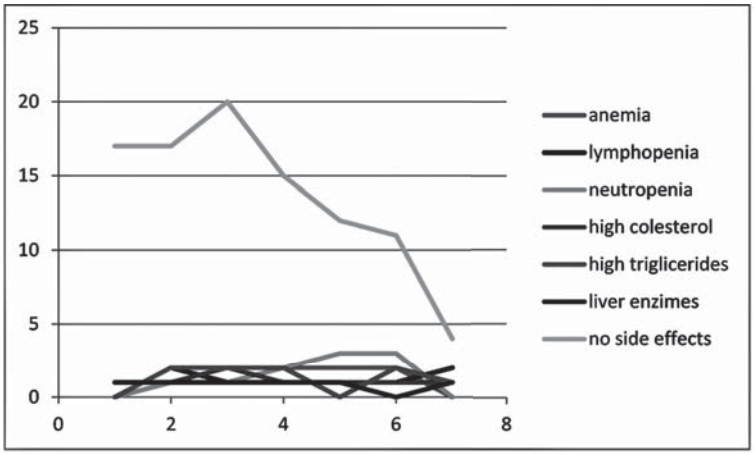

Figure 3. *Side effects for 6 years treated patients.*

of treatment lasted 7 years. The figure below depicts the fact that the side effects fluctuated during the whole period. There are periods with a few cases and other periods with much more side effects cases. Beyond these, the total cases of patients with no side effects decrease significantly during the whole period. More specifically, at the beginning of the treatment there were 8 patients with no side effects, when in the end there were only four with no side effects.

Secondly, we will deal with those patients whose period of treatment lasted 6 years. Specluating the figure below is obvious that the side effects fluctuate during the whole period, but there seems to be an increase of the side effects such as decreased neutrophils levels and liver enzimes. Beyonf this, the total cases of patients with no side effects have a decrease during the period of the third to the sixth year.

Finally, we will deal with those patients whose period of treatment lasted 3 years. Examining the figure below is obvious that the side effects are mostly stable. The total cases of patients with no side effects decreased from 12 to 10. Because of the small period of time (3 years) we cannot exclude reliable and unbiased results, but all side effects seem to be stable.

Discutions

First of all, after the primary statistical analysis we concluded that our group of patients was an omogenous one and that it reflected the literature in matters of age and sex. Although we have examined a lot of parameters in this group, in this article we will refer to associated pathology and to the side effects of the immunomodulatory treatment. Until the first year of treatment the EDSS score seemed to be quite stable. However, with slight fluctuations the EDSS score started to mildly increase up to 2,63 in the seventh year of treatment, results that were similar to the literature. The statistical significance is not important and thus, we presume that the EDSS score remained stable during all years of treatment with a slight tendency of increasing, but did not influenced the associated pathology or the side effects of the treatment. Also, the duration of the treatment did not influenced the EDSS score in any administrated medication of this study.

Concerning the associated pathology that was observed in our patients during the years of treatment, it is documented that 53,7% of the total sample presented an additional pathology. The most frequent of all was dyslipidemia, which reached the percentage of 25,3%, followed by hyperglycemia

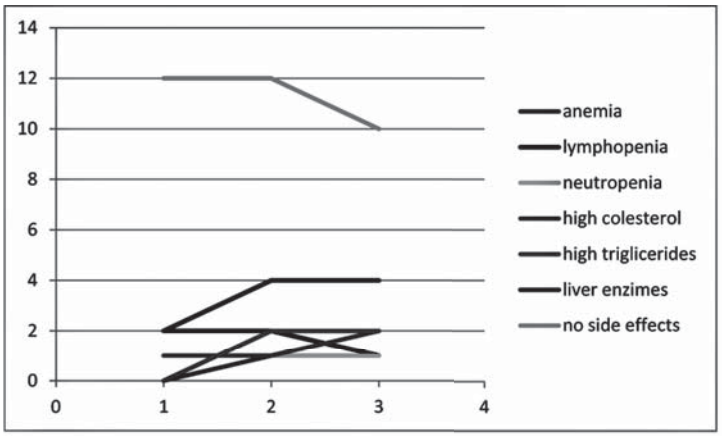

Figure 4. *Side effects for 3 years treated patients.*

(8,7%). Vertebral hernias in cervical or lumbar spinal column, associated with laminectomies or spondylofussion was found in 6% of our patients. Further, 4% of them were suffering from arachnoid cyst and iron deficiency anemia. The one in 6 patients with arachnoid cysts developed epileptic convulsions during the fourth year of treatment. However, his EDSS score or his annual relapse rate was not influenced by the underlying disease. Hereditary diseases like Gilbert syndrome, Charcot Marie Tooth Neuropathy and Venous Insufficiency were also recorded, as well as idiopathic diseases like Raynaud syndrome. Finally, there were also one case of infection with H1N1 virus, Hepatitis B, Lyme disease and tuberculosis.

Another interesting point of the comorbidities analysis is the metabolic diseases. As it is already mentioned, 25,3% of the patients developed dyslipidemia and 8,7% hyperglycemia. Additionally, three patients of our group were obese and on the other hand another two women lost a lot of kilos during the first year of treatment. However, we cannot correlate a specific medication with the metabolic syndrome, since approximately the actual numbers of medication and dyslipidemia or hyperglycemia are the same. After detailed analysis of the EDSS score in relation to the associated pathology, it is concluded that the EDSS score is not influenced by the existence of other than MS disease, either hereditary or idiopathic, or metabolic, neoplasias, vascular disease and infections.

As regard to side effects, the group of patients with seven years of treatment, does not present side effects in the first year of treatment. However, as time goes by, side effect's percentage rise. Anemia, raised liver enzymes and dyslipidemia are the most common side effects. In patients who were treated for 6 years, the side effects appearance seem to rise over time. Adverse events like decreased neurtrophilia and increased liver enzymes are most often met, followed by anemia and dyslipidemia. In the 3 years treated group of patients, the side effect free number of cases seems to decrease through the years. Thrombocytopenia and raised liver enzymes are the most commonly met pathological side effects. However, it is estimated that in this specific group of patients the side effects remain stable.

Summarizing the results of the side effects, it seems that as time of treatment rises, the side effects free patients decrease in actual number. The most frequent side effects are anemia, thrombocytopenia, raised liver enzymes, dyslipidemia, lymphocitopenia and neurtropenia. As to anemia, it is a mild one, with no significantly decrease haemoglobin and hematocrit levels. The same is observed with the liver enzymes, while the increase in SGOT and SGPT values are 40% increase in comparison with the maximum accepted normal value.

Conclusions

Multiple sclerosis is a chronic, inflammatory demyelinating, neurodegenerative disease of the central nervous system, that affects the young adult and is associated with a high degree of disability if not treated. There is no curable treatment but the immunomodulatory one is aimed in decreasing the relapse rate and the disability following the relapse. Physical and mental comorbidity and adverse health behaviors are common in patients with MS. Comorbidities and health behaviors are associated with adverse outcomes in MS and should be considered in the assessment and management of patients with MS.

The group of patients we analysed corresponded to the available literature in matters or number, age and sex. We concluded that dyslipidemia was the most common comorbidity, followed by hyperglicemia and vertebral hernia. The presence or not of a comorbidity before the treatment does not relate to the EDSS score ($p<0.05$). Thus the presence or not of an associated pathology during 7 years of immunomodulatory treatment does not affect the patient's EDSS score and disability.

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