12th Int. Workshop on Generalized Nets
Burgas, Bulgaria, 17 June 2012, 32–38

Generalized net model for diagnosis of multiple sclerosis

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Abstract: Multiple sclerosis (MS) is a socially significant disease with complex etiology and pathogenesis. The diagnosis of MS is based on clinical, MRI and paraclinical criteria, but pathognomonic test for the disease is not yet detected. This makes the process of diagnosis suitable for modeling with generalized nets [1]. The present work proposes such generalized net model.
Keywords: generalized net model, multiple sclerosis, MacDonald criteria
AMS Classification: 68Q85.

1 Introduction

MS is a socially significant disease that affects a high percentage of active population depending on the geographic latitude. The most commonly affected are Caucasian. [6, 7]. Bulgaria is located in the region with high prevalence which makes the problem of early diagnosis and correct therapeutic approach particularly actual. The etiology and pathogenesis of MS are not fully understood. Diffuse regions of white matter are affected as a result of axon demyelinisation. Perivenous inflammation and later- degeneration of neurons in the gray matter occur. The clinical course of disease is individual, which further impede clinicians in the diagnosis and prognosis.

Despite numerous studies in this area, pathognomonic test for the disease in still not known. The diagnosis of MS is complex. It is based on clinical, MRI and paraclinical criteria. The assessment is individual, taking into account the MacDonald criteria [4]. These criteria were established in 2001 and till the present moment they are revised 3 times, which indicates that the diagnostic searching are still in a process.

Three main forms of the disease are known depending on its clinical course:

- Relapsing-remitting MS;
- Secondary progressive MS, which is usually a consequence of relapsing-remitting MS;
- Primary progressive MS.

The most common is relapsing-remitting form of MS (RRMS). It is manifested by clearly defined relapses (attacks) and remissions between them. An 'attack' is determined as appearance of neurological deficit, which persists more than 24 hours and is not preceded by fever of infection. The interval between the relapses should last at least 30 days. Other reason for the symptomatic should be excluded.

Early defining of the form of disease is essential for the choice of immunomodulating therapy.

The diagnosis of MS requires elimination of many similar diagnoses, also demonstration of dissemination in time and dissemination in space.

Dissemination in space is determined as ≥ 1 T2 lesion/s in at least 2 of the four typical areas of the central nervous system – periventricular, juxtacortical, infratentorial and cervical myelon. Dissemination in space is defined as appearance of a new T2 lesion/lesions with/without contrast enhancing visualized in further MRI compared to the results of the initial MRI, irrespective of time interval, or a simultaneous presence of asymptomatic lesions with/without contrast enhancing at the particular study.

Diagnosis of MS according to latest revision of MacDonald criteria [4] is based on the following general algorithm.

First relapse

- Objective clinical evidence of at least 1 lesion (clinically isolated syndrome, CIS). On this basis it is necessary to perform MRI of brain and cervical myelon;
- Additional criteria for diagnosis:
  - At least one T2 lesion on MRI with typical localization (periventricular, juxtacortical, infratentorial and cervical myelon.), [2];
  - Supporting criteria – prolonged latencies of evoked potentials [2, 3]; oligoclonal bands and/or increased IGG index from CSF; findings in ophthalmological tests: temporal pallor of the papilla, scotomas in perimetry, impaired color vision, disturbed contrast visual acuity or specific finding in OCT (optic coherent tomography);
- Lack of other condition which could explain the existent pathology.

Conversion to MS

- **Second relapse:** Objective clinical evidence of 2 or more lesions. In this case additional evidence is not mandatory, but is desirable;
- **No second attack (only one relapse):** MS conversion could be discussed in the following cases:

- If there is an objective clinical evidence of 1 lesion and MRI has found: at least 1 T2 lesion in at least 2 of the typical regions (dissemination in space) and co-existence of asymptomatic lesion (with/without contrast enhancing) or new T2 lesion with/without contrast enhancing in further MRI irrespective of the time of performance (dissemination in space) .
- If there is an objective clinical evidence for more than 1 lesion is sufficient only dissemination in time or only dissemination in space

- **Supporting criteria:** Prolonged latencies of evoked potentials; oligoclonal bands and/or increased IGG index from CSF; findings in ophthalmological tests: temporal pallor of the papilla, scotomas in perimetry, impaired color vision, disturbed contrast visual acuity or specific finding in OCT;
- Lack of other condition which could explain the existent pathology.

Primary-progressive MS

Usually is manifested with insidious neurological progression without clear defined relapses. Progression should be observed for the period of at least one year. The clinical assessment is made retrospectively or prospective. At least of the following 3 criteria should exist:

- 1 or more T2 lesion/lesions in one of the following regions|: periventricular, juxta-cortical, infratentorial (dissemination in space);
- 2 or more 2 T2 lesions in the myelon (dissemination in space);
- positive result from the CSF test.

Before establishing the definite diagnosis of relapsing-remitting MS is necessary to register at least one attack in neurological examination, supported by pathologically changed visual evoked potentials in patients, reporting visual disturbances or MRI data for demielyn-ating lesions in the typical regions according to neurological symptoms .

Clinical diagnosis, based on objective clinical finding for 2 attacks is more accurate. History of experienced attack in the absence of documented objective neurological finding can be considered for initial demyelinating event, but at least one attack needs to be confirmed in objective measurements.

In patients who experienced 2 or more relapses where there is objective clinical evidence for 2 or more lesions additional tests are not mandatory according to diagnostic criteria of MacDonald. But it is desirable the diagnosis definitive MS to be based also on the results of paraclinical findings, particularly:

- Oligoclonal bands in CFS electrophoresis and/or elevated IGG index;
- Prolonged latencies in different modalities evoked potentials (highest sensitivity have prolonged latencies in visual evoked potentials), [3];
- Specific findings from the ophthalmoneurological examination: temporal pallor of papilla, scotoma in perimetry, impaired color vision, impaired contrast visual acuity, OCT.

If none of the paraclinical results is not positive, the diagnosis of MS should be reviewed and all registered symptoms and imaging findings have to be analyzed again by searching an alternative diagnosis.

2 GN model

A GN model is presented on Figure 1. The initial characteristic of the token α in place L_1 is *"Patients data"* – preliminary data from all of the performed examinations.

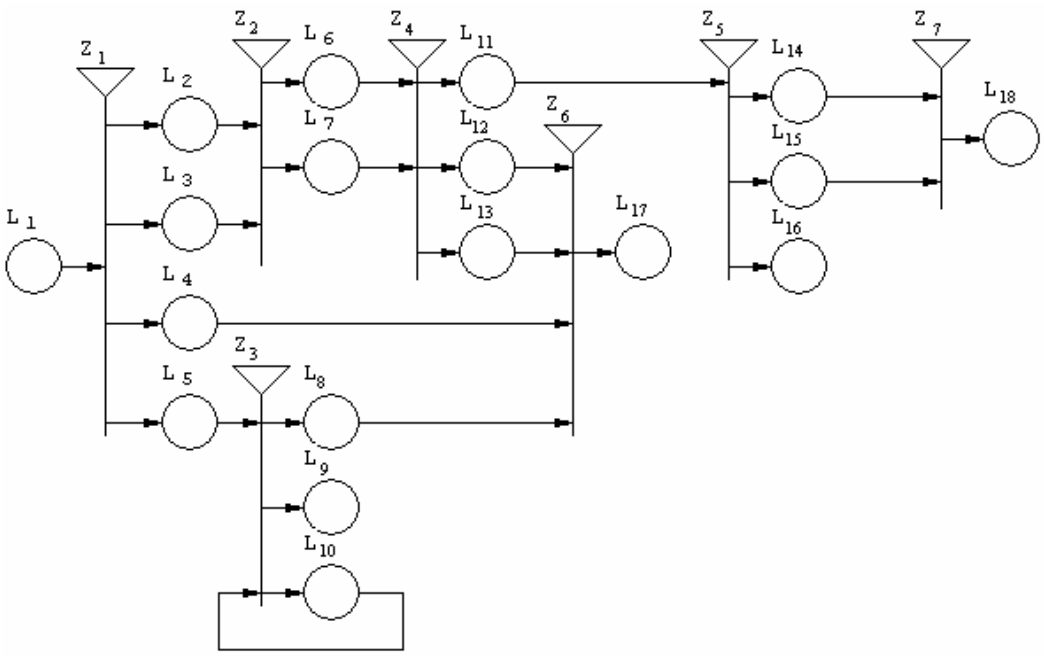

Figure 1: Generalized net model for diagnosis of multiple sclerosis

$$Z_1 = \langle \{L_1\}, \{L_2, L_3, L_4, L_5\}, r_1 \rangle,$$

where:

$$r_1 = \begin{array}{c|cccc} & L_2 & L_3 & L_4 & L_5 \\ \hline L_1 & W_{1,2} & W_{1,3} & W_{1,4} & W_{1,5} \end{array},$$

- $W_{1,2}$ = *"Objective clinical evidence of* 1 *lesion – first relapse"*;
- $W_{1,3}$ = *"Objective clinical evidence of* ≥ 2 *lesions – first relapse"*;
- $W_{1,4}$ = *"No objective clinical evidence of a lesion"*;
- $W_{1,5}$ = *"Lack of distinct attack"*.

$$Z_2 = \langle \{L_2, L_3\}, \{L_6, L_7\}, r_2 \rangle,$$

where:

$$r_2 = \begin{array}{c|cc} & L_6 & L_7 \\ \hline L_2 & W_{2,6} & W_{2,7} \\ L_3 & W_{3,6} & W_{3,7} \end{array},$$

- $W_{2,6} = W_{3,6}$ = *"It is necessary to perform MRI"*;
- $W_{2,7} = W_{3,7}$ = *"It is necessary to conduct supportive investigations"*.

$$Z_3 = \langle \{L_5, L_{10}\}, \{L_8, L_9, L_{10}\}, r_3 \rangle,$$

where:

$$r_3 = \begin{array}{c|ccc} & L_8 & L_9 & L_{10} \\ \hline L_5 & W_{5,8} & W_{5,9} & W_{5,10} \\ L_{10} & W_{10,8} & W_{10,9} & W_{10,10} \end{array},$$

- $W_{5,8} = W_{10,8}$ = *"No progression of symptoms over 1 year"*;
- $W_{5,9} = W_{10,9}$ = *"Insidious progression of symptoms"*
  That is the progression of the disease at least one year, clinically evaluated retrospectively or prospectively, and at least 2 of the following 3 criteria:
  - 1 or more than 1 T2 lesion/lesions in any of the following areas: peri-ventricular, juxtacortical, infratentorial (dissemination in space);
  - 2 or more than 2 T2 lesion/lesions in the myelon (dissemination in space);
  - positive result of CSF test;
- $W_{5,10} = W_{10,10}$ = *"It needs observation of the patient for at least 1 year"*;

In place L_9 the token α receives characteristic *"The patient suffers from primary progressive MS"*.

$$Z_4 = \langle \{L_6, L_{10}\}, \{L_{11}, L_{12}, L_{13}\}, r_4 \rangle,$$

where:

$$r_4 = \begin{array}{c|ccc} & L_{11} & L_{12} & L_{13} \\ \hline L_6 & W_{6,11} & W_{6,12} & W_{6,13} \\ L_7 & True & True & True \end{array},$$

- $W_{6,11}$ = *"There is evidence of demyelinisation in typical regions"*;
- $W_{6,12}$ = *"No registered evidence of demyelinisation in typical regions"*;
- $W_{6,13}$ = *"No other reason for the attack is found"*.

$$Z_5 = \langle \{L_{11}\}, \{L_{14}, L_{15}, L_{16}\}, r_5 \rangle,$$

where:

$$r_5 = \begin{array}{c|ccc} & L_{14} & L_{15} & L_{16} \\ \hline L_{11} & W_{11,14} & W_{11,15} & W_{11,16} \end{array},$$

- $W_{11,14}$ = *"Objective clinical evidence of at least 1 new lesion" OR "Both dissemination in time and dissemination in space" OR "Objective clinical evidence of at least two lesions and dissemination in space or dissemination in time"*;
- $W_{11,15}$ = *"Necessary to do supporting studies"*;
- $W_{11,16} = \neg W_{11,14}$.

In place L_{16} the token α receives characteristic *"The patient's diagnosis is CIS"*.

$$Z_6 = \langle \{L_4, L_8, L_{12}, L_{13}\}, \{L_{17}\}, r_6 \rangle,$$

where:

$$r_6 = \begin{array}{c|c} & L_{17} \\ \hline L_4 & True \\ L_8 & True \\ L_{12} & True \\ L_{13} & True \end{array},$$

In place L_{17} the token α receives characteristic *"The patient does not suffer from MS"*.

$$Z_7 = \langle \{L_{14}, L_{15}\}, \{L_{18}\}, r_7 \rangle,$$

where:

$$r_7 = \begin{array}{c|c} & L_{18} \\ \hline L_{14} & True \\ L_{15} & True \end{array},$$

In place L_{18} the token α receives characteristic *"Conversion into relapsing remitting MS"*.

Conclusion

Sufficiently reliable criteria for diagnosis of multiple sclerosis are not yet established because of the complex and not fully understood pathogenesis, diffuse localization of lesions, individual course of the disease and lack of specificity, [5]. In the proposed generalized net model, the most actual trends in the diagnosis of MS are included. In further revisions of the MacDonald criteria, the model would be updated, which would allow to minimize errors in the diagnostic process.

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