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Original Research

Fractal analysis in the quantification of medical imaging associated with multiple sclerosis pathology

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Abstract

Backgrounds: Multiple sclerosis (MS) is an inveterate phlogistic situation characterized by focal and vaguely diffusive de-myelination and neurodegeneration, in the sphere of central nervous system (CNS). The brain's chronic inflammatory reaction includes astrocyte stimulation and microglial motivation, as well as macrophages marginal conscription. This lasting serious soreness of the brain is connected with neurodegeneration period and disability advance. **Methods**: The present study is considering two main purposes as follows. Primarily, to apply the fractal analysis in the idea of documenting the fractals dominance at all stages of the nervous system hierarchy, giving faith to the precept of their funciar relevancy. Secondly, to take into account the problems unresolved of the thorough connections between self-organized criticality concept and self-similarity notion. More precisely, in reality we will obtain information about the fractal size and lacunarity of magnetic resonance imaging (MRI), on the areas of interest of the brain, rich in microglial cells with fringes from peripheral macrophages cells. **Results**: This approach will play a decisive role in the action of detecting neural disabilities, such as in particular multiple sclerosis cortical onset, the final goal of our investigation. The diagnosis is based on interpretation of both histological sample pictures and images obtained by nuclear magnetic resonance. Using fractal analysis, we have calculated, for each image separately, both the fractal dimension and the lacunarity, as an objective quantitative measure of the demyelinating action. **Conclusions**: For three histopathological samples on glial cells, with visible erosions, the fractal dimension has value over 1.89 and the lacunarity value is between 0.050 and 0.079. In the gray level stages of the studied MRI pictures, the fractal dimension is above the value of 1.7 and the lacunarity is between the values of 0.0286 and 0.0393.

Keywords: fractal analysis; lacunarity; box-counting; microglial inflammation; multiple sclerosis

1. Introduction

Multiple sclerosis is a demyelinating disorder in which myelin sheaths, the substance that covers most nervous fibers, as well as nerves, especially the optic nerves and structural elements of the spinal cord, are damaged or destroyed. Worldwide, approximately 2.5 million people have multiple sclerosis, and in Romania, there are over 10,000 patients diagnosed with this condition.

The term "multiple sclerosis" refers to several areas of scarring observed, namely the sclerosis itself, which results from the destruction of the sheath around the nerves. This destruction is universally called demyelination. Sometimes the nervous fibers that send the messages (axons) are also affected. Over time, the brain may shrink (brain atrophy) due to axonal damage [1].

The disease usually progresses through an alternation of periods of relative health with episodes of worsening symptoms—through outbreaks or recurrences. Affected people may experience abnormal vision problems and new sensations, and movements may be slow and inaccurate, affecting coordination.

The diagnosis is based on symptomatology, clinical examination results and medical imaging, by magnetic resonance imaging, the so-called MRI. If we talk about the causes of this serious disease, they remain unknown in general, but a possible explanation would be early exposure to a virus (possibly a herpetic virus or retrovirus) or an unknown substance, which somehow triggers the immune system reaction, to attack one's own tissues (autoimmune reaction).

Genetic predisposition may be involved in the onset of multiple sclerosis. For example, a parent, brother or sister with multiple sclerosis increases the risk of acquiring the disease. In addition, multiple sclerosis is more likely to develop in people with certain genetic markers on the cell surface, called human leukocyte antigen. Normally, these markers help the body distinguish its own cells from the "nonself" ones, in order to know which ones it can attack.

In conclusion, multiple sclerosis is a progressive disease that affects the central nervous system (CNS) and is usually diagnosed in young adults, who are between 20 and 40 years old. However, the condition can be triggered at any time between the ages of 15 and 60, and statistics show that, in the world, the number of women suffering from this disease is higher than that of men.

In this article, we will analyse medical images that show the effects of multiple sclerosis on nervous matter using fractal analysis. More precisely, we will calculate, for each image separately, or for representative pieces of it, both the fractal dimension and the lacunarity, as an objective quantitative measure of the demyelinating action produced in time.

Functional capabilities in the service of the human brain can be described as having a fractal shape due to the multiple connections between neurons and microglia (small cells with rich branches to protect neurons against pathogens and accumulate cell debris, having a phagocytic role) [2]. This type of cellular topology apparently has a chaotic aspect, but, nevertheless, through the possibilities offered by modern computer programs, this case can no longer be a problem [3].

Neurons and microglia have a similar structure, usually centrally elongated, and perform almost the same processes, but there is a significant difference between the morphologies of these cell types. In an adult human body, microglia are smaller than the neurons to which they are assigned. They have a distribution throughout the central nervous system, being placed predominantly in the gray matter, as a satellite of neurons and blood vessels, rather than in white matter, where they are more of a prefibrillar satellite.

Usually, microglia are located in the vicinity of neural processes, moving rapidly and constantly, carrying out their own processes, one significant being the elimination of synapses of neurons that have exceeded their utility to make room for fresh and efficient synapses [4]. Moreover, the microglia occasionally adopt an unbranched morphology to perform certain tasks [5].

It is possible that many correct things can be reported about a cellular network at a glance through a microscope, but the precise determination of a diagnosis must be based on a firm process of analysis in which the experience of neurologists must be complemented by computers. It thus becomes a priority to develop specialized software that can quickly read neural images to establish some appropriate specific assessment as a quantitative measure of the microstructural analysis (now at pixel level) performed.

2. Materials and methods

According to specialized monographs, nervous tissue consists of neurons and glial cells, which have a common origin from the outer envelope of the embryo. Glial cells are a type of non-excitable cells, small in size, but much more numerous than neurons, the parity established by neuroscience experts being one neuron per 50 glial cells. The fact that glial cells are a type of mitotic cells, with trophic purpose, also gives them the functions of protection and metabolic control of neurons. Moreover, they guarantee the isolation of neurons in terms of their electrical emission, as the neurons are not allowed to interfere. The connections between glial cells are made by communicating junctions and not by synaptic contacts [4].

There were processed three different images of histological samples, in which there are presented lesion edges specific of multiple sclerosis disease. Histology of immunopathological patterns is illustrated in the three different photographs presented in the paper, to exemplify the pathologic heterogeneity of primary demyelinating manifold sclerosis of abnormal tissue zone, practically an area with obvious lesions.

In other words, myelin-associated glycoprotein damage in the first photography is representative for pattern evident lesions. As a conclusion of what each photo represents, we can now state that myelin-associated glycoprotein is lost in the first image, whereas myelin oligodendrocyte glycoprotein is again present in the lesion areas for the second, whilst in the third photo the small lesions are infiltrated by not a few macrophages.

Fractal analysis of both histological sample pictures and images obtained by nuclear resonance was used as the working method. Object-based Image Analysis (OBIA) technique was used to determine the lacunarity [6]. This is one of the more unlike procedures developed to defeat the limitations of the pixel-based paths. It integrates textural, spectral and contextual acquaintances to identify thematic classes from a picture. The first demarche in OBIA is to segment the picture frame into homogeneous geometrical items/pieces, more precisely by associating together the pixels in well-defined vector objects.

In the analysis performed in continuation, three images obtained by nuclear magnetic resonance were used. Magnetic resonance imaging aspects of pattern lesions with atypical ringlike enhancement will be interpreted with appropriate methods, presented below. For a start, it can be said that from them it is observed that all three patients with a ringlike increase pattern showed atypical features, as demonstrated in these pictures, noted with A, B and C. That was one of the reasons they were chosen. Each of the photos indicated above has undergone two degrees of primary processing (digital manufacture of the original image), up to the stage of gray levels, necessary to apply the box counting procedure [7], which leads to the numerical evaluation of the fractal size and the lacunarity.

Note. We mention that all these photographs analyzed in the paper, both those of histological samples and those obtained by nuclear resonance, were taken from free sources, more precisely from an open access journal type, the bibliographic reference to the journal in question being introduced immediately below their presentation in our paper.

2.1 Fractal analysis of microglia

As with neurons, several papers have been published over time describing the use of fractal analysis in the study and classification of microglia morphology in neuroanatomy, pathology, and development in time of the initial neurological disease observed [8].

One difference between the two fields of fractal analysis of neurons and microglia is that the fractal size of microglia has been more clearly correlated with its function. Using the box-counting algorithm, it has been shown that, in principle, microglia in a normal, healthy brain are strongly branched with a relatively high value of D_B [8]. Here D_B is fractal dimension calculated through box-counting method [9]. In response to certain stimuli, such as chronic stress, they can hyper-branch up to a condition with a D_B as high as possible. Moreover, when they respond to completely harmful pathological events, such as brain trauma, they enter a de-branching cycle that involves the concomitant decrease of D_B, and then return through a cycle of re-branching and growth of D_B when they resume their normal activity [10].

Along with the fractal dimension, lacunarity and multifractal analysis were used to classify the morphology of microglia. In particular, lacunarity was used to objectively distinguish between very similar microglial morphologies within an activation category and which have the same D_B value [10]. *In Silico* modeling has shown that D_B is more sensitive to structures with rich ramifications, so lacunarity has become the accepted solution for determining particular characteristics that are not always visually recognized.

Nota bene. In silico modelling is a logical expansion of regulated *in vitro* laboratory routines.

2.2 Fractal dimension and lacunarity

The fractal dimension was useful for quantifying not only the gross pathological responses, but also the more difficult to observe responses in different regions of the brain after transient global ischemia. This general ability to quantify the subtleties of microglial morphology has important implications, because microglia are immuno-inflammatory cells, but not only, these cells having multiple roles in maintaining the normal structure and function of the brain, interacting with all parts of the neuron. For example, the morphological complexity of a microglia can be quantified using the fractal dimension.

Over time, scientists have struggled to develop new methods for calculating fractal dimension and gaps influence such as the box-counting algorithm. In fact, this method is suitable for measuring the fractal dimension of different types of inputs, using a number of predefined square or rectangular shapes to cover the object. Then it counts the total number of boxes needed to cover all non-zero elements of the object. The determined dimension is also known as the Minkowski-Bouligand dimension or the Kolmogorov dimension [11].

They are involved in the cutting rods, facilitating synaptic transmission, interaction with the extracellular matrix and axonal excitability. They secrete growth factors and play important roles in treating stress on all levels, from sleep deprivation to subtle cognitive experience or to modulating severe pain and trauma. In this regard, many roles of microglia in the normal functioning of the brain and subtle dysfunctions are currently being investigated, suggesting that the fractal dimension of microglia will be applicable in many areas (e.g., treatment monitoring, learning, stress, alcoholism and schizophrenia) [12]. From the fractal theory, it is known that the level of details would remain unchanged, respectively infinite for an authentic fractal.

Regardless of how the box-counting algorithm is implemented, the degree of gaps, known as lacunarity, will be calculated starting from the probability distribution of pixels, also known as mass distribution [13]. The number of pixels per box will determine the distribution of pixels depending on the size of the box or the scale (ε), a value that is inversely proportional to the size of the box. For a certain value (ε), the degree of lacunarity will be denoted

$$\lambda_\varepsilon = (CV)^2 = \left(\frac{\sigma}{\mu}\right)^2 \tag{1}$$

where σ represents the standard deviation and μ the average of the pixels per box as a function of the value ε.

To arrive at a single value for λ, all values of λ_ε can be summarized as the average $\bar{\lambda}$ for the number of calibrations E used

$$\bar{\lambda} = \frac{\sum \lambda_\varepsilon}{E} \tag{2}$$

The mean of Λ for the number G of frames in the grid applied over the image can be determined as a measure of the degree of lacunarity as follows:

$$\Lambda = \frac{\sum_{y=1}^{G} \bar{\lambda}_y}{G} \tag{3}$$

From Eqn. 3 it can be seen that, for a higher value of λ, a greater variation in the distribution of pixels in an image will be obtained. If $\lambda > 1$, σ generally exceeds μ which implies that there are very large and very small groups of pixels or there is considerable heterogeneity in an image. Conventional pixel-based picture sorting confers to a certain field a singular category per any pixel. In fact, every pixel has the same dimension, an identical format and it does not have any intention to be different from each other [14]. Thus, the process unfolded of pixels segmentation/clustering which takes place is the one carried out in Object-based Image Analysis (OBIA) technique, at the pixel scale.

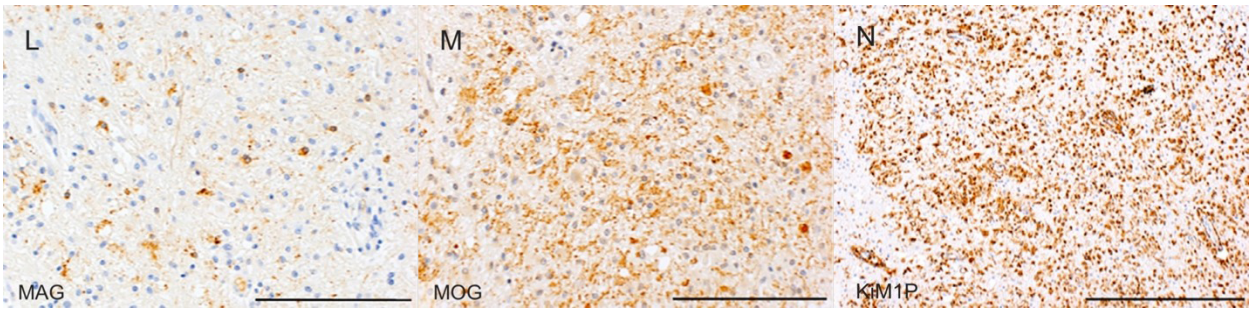

Fig. 1. Images of histological samples in three pictures (L, M, N), with different lesion edges.

Fig. 2. Original photo L ($\times 10^4$) together with the two stages of digital processing image. The second picture is the black and white representation and the third picture is the grey level representation of the original photo L.

Fig. 3. Original photo M ($\times 10^4$) together with the two stages of digital processing image. The second picture is the black and white representation and the third picture is the grey level representation of the original photo M.

3. Results

Untimely acting demyelinating lesions signify the hasty lesion phases and are a premise of immuno-pattern assortment. These visible erosions have been arranged in classes in one of the known immuno-pathological models, Fig. 1. The damaged surface margin was classified as either a pointed or undefined edge, depending on its visual appearance. In completion to the description, a boundary attendance of macrophages, pretended to be as a macrophage's accumulation on the lesion margin, was observed.

In Fig. 1, in three different images (the first marked with L, the second with M and the third with N) of histological samples, are presented lesion edges specific of multiple sclerosis disease [15]. The photos of histologies (L, M, N) are considered and presented to illustrate morbid heterogeneity of untimely dynamic demyelinating multiple sclerosis denudation.

In contraposition, in (L, M) histologies, Myelin-Related Glycoprotein (MAG) loss (L) is characteristic for this erosion model. MAG is lost (see L), since Myelin-Oligodendrocyte Glycoprotein (MOG) (see M) is yet current in lesion zones. The present destruction areas of the myelin (see N) are infiltrated by many macrophages (KiM1P).

Neuropathological analyzes are now considered successful after applying fractal analysis to appropriate images. This will be done in continuation of our approach. The obtained results, regarding the fractal dimension and lacunarity, are subsequently enumerated in presentation. For each photo, individually, we have the following values, listed below, respectively under each of the three photos.

Fig. 4. Original photo N ($\times 10^4$) together with the two stages of digital processing image. The second picture is the black and white representation and the third picture is the grey level representation of the original photo N.

The first original photograph L, Fig. 2, has the values $d_1 = 1.8986 \pm 0.078868$ and the lacunarity $\Lambda = 0.0792$. The second original photograph M, Fig. 3, has the values $d_2 = 1.8981 \pm 0.07891$ and the lacunarity $\Lambda = 0.0596$. The third original photograph N, Fig. 4, has the values $d_3 = 1.9109 \pm 0.07012$ and the lacunarity $\Lambda = 0.0502$.

The solid black line present on the photo is drawn to make the connection with the scale at which the image is taken. Thus, the scale bar in photo is 10^{-2} m and it represents 10^2 μm in reality. In terms of image magnification, respectively magnificence of photography, it represents a magnification of 10^4 times.

Figs. 2,3,4 show the stages of processing the original photographs of histological samples of microglia, differentiated by their appearance/pathology. Starting from the original photo (first photo) there are two more stages of digital image processing, respectively the transformation of color images into black and white images, the first stage (middle photo) and the rectangular coverage of the surface, the second stage (the last photo in the triptych). From the last photo, the fractal dimension and the lacunarity are calculated by the box-counting method.

In Fig. 5, all three patient images with a ring-like increase model presented nontypical characteristic, as the photos themselves demonstrate [15]. Y. Miki makes a detailed study on MRI, more precisely a complete Review Article, with reference to demyelinating diseases and its diagnosis, in the paper [16].

Fig. 6 shows the two degrees of digital processing of the original image A, up to the stage of gray levels, necessary to apply the box counting procedure, which leads to the numerical evaluation of the fractal dimension and the lacunarity [17]. The first original photograph, identified with the super script A, has the fractal values $d_1 = 1.8164 \pm 0.072267$ and the lacunarity $\Lambda = 0.0354$.

Fig. 7 is the special 3D Voxel representation for image A.

Fig. 8 shows the two degrees of digital processing of the original image B, up to the stage of gray levels, necessary to apply the box counting procedure, which leads to the numerical evaluation of the fractal size and the lacunarity.

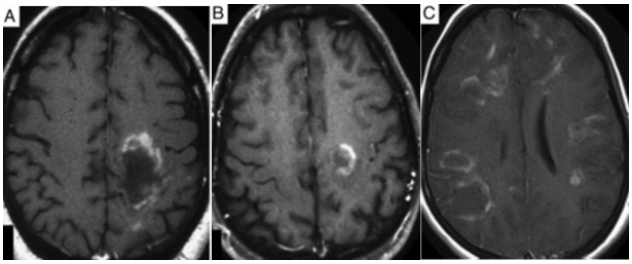

Fig. 5. MRI (Magnetic Resonance Imaging) features of conventional lesions with unusual ring-like accumulation, in three distinct pictures (A, B, C).

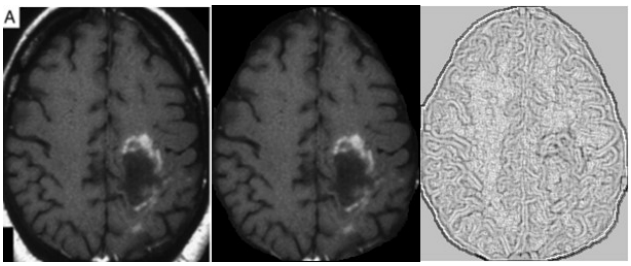

Fig. 6. Picture A of MRI cerebral and the two stages of digital processing image. The second picture is the black and white representation and the third picture is the grey level representation of the original photo A.

The second original photograph, identified with the super script B, has the fractal values $d_2 = 1.7867 \pm 0.060652$ and the lacunarity $\Lambda = 0.0393$.

Fig. 9 is the special 3D Voxel representation for image B.

Fig. 10 shows the two degrees of digital processing of the original image C, up to the stage of gray levels, necessary to apply the box counting procedure, which leads to the numerical evaluation of the fractal size and the lacunarity. The third original photograph, identified with the super script C, has the fractal values $d_3 = 1.8298 \pm 0.028899$ and the lacunarity $\Lambda = 0.0286$.

Fig. 11 is the special 3D Voxel representation for image C.

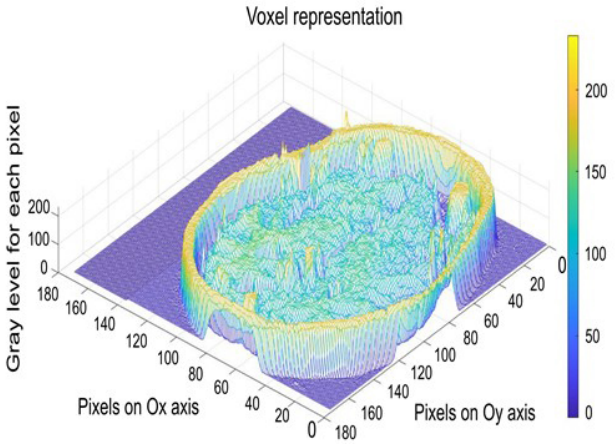

Fig. 7. 3D Voxel representation for image A, the latest version with shades of gray.

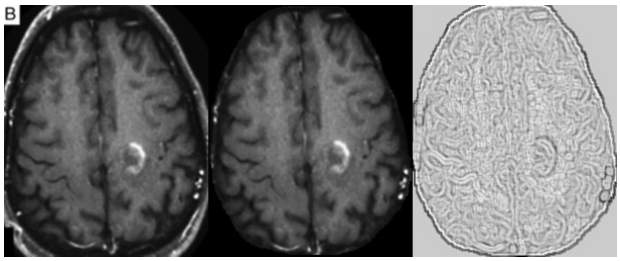

Fig. 8. Picture B of MRI cerebral and the two stages of digital processing image. The second picture is the black and white representation and the third picture is the grey level representation of the original photo B.

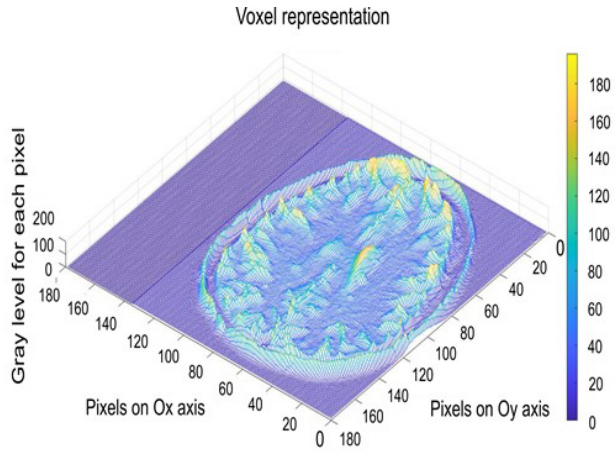

Fig. 9. 3D Voxel representation for image B, the latest version with shades of gray.

Concerning Figs. 7,9,11, the latest versions with shades of gray, a presentation in detail will take place in the next chapter, named Discussion.

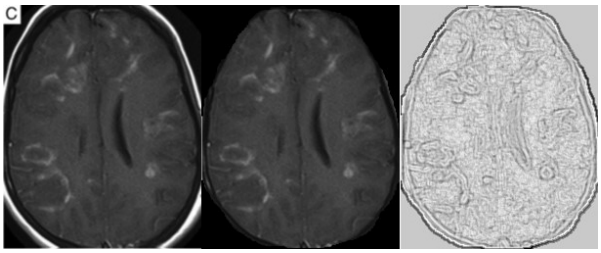

Fig. 10. Picture C of MRI cerebral and the two stages of digital processing image. The second picture is the black and white representation and the third picture is the grey level representation of the original photo C.

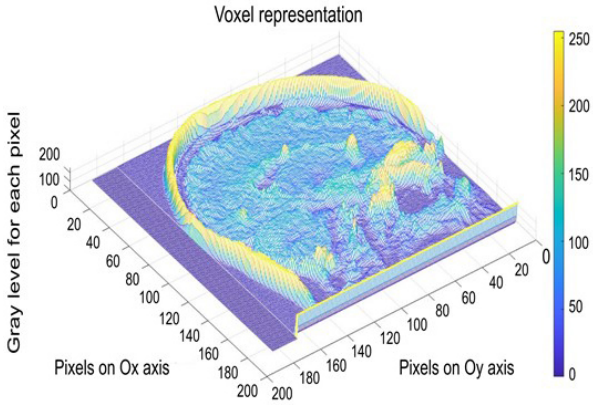

Fig. 11. 3D Voxel representation for image C, the latest version with shades of gray.

Note. Voxels are frequently used in the attempt to visualize-read a planar image, the quantitative analysis of visualization and in the expression of specific scientific data in medical imaging. The word voxel comes analogously to the word "pixel", with "vo" representing "volume" and "el" representing "element".

4. Discussion

Neuropathological analyzes of Figs. 2,3,4 are now considered successful after applying fractal analysis to appropriate images [18]. It is observed that we can obtain a "formula" for calculating the dimension by dividing the object into self-similar copies, squares or rectangles, each N times smaller than the initial object. This was done successfully in the last image of each figure, with the numbers 2, 3 and 4. If P is the number of copies thus obtained, then the fractal dimension can be estimated with the correct formula $D = logP/logN$ [19]. However, the edited formula is valid to the second decimal place for the (considered simpler) examples above.

The fractal dimension has very high values, over 1.89, immediately close to the value of 2, (calculated for a flat surface in Euclidean geometry), the maximum value allowed mathematically. The value of the lacunarity is between 0.050 and 0.079, values that are a bit low to highlight

the condition we are talking about here. This is explained by the fact that the erosion present in the image illustrates the morbid heterogeneity of untimely dynamic demyelinating multiple sclerosis denudation. Obvious for everyone it is the fact that this process is at the beginning, just initiated, but it takes place in the whole brain mass, being present on the whole surface of the image.

In the magnetic resonance pictures given out in Fig. 5, the pattern characteristics of type III lesions, with similar unusual annular, are highlighted. Every one of the three people suffering from a type III neurological disease, with an annular similar pattern, have manifested unusual attributes and are presented in three images, these being the A, B and C photos. Thus, in this figure, MRI (Magnetic Resonance Imaging) features of conventional brain lesions with uncommon ring-like accumulation, as the photos of all patients themselves demonstrate, are presented [15].

The fractal dimension in all the studied images of Figs. 6,8,10, found out each in the gray level stages, is above the value of 1.7, so quite close to the value of 2, which is the maximum value allowed mathematically. The lacunarity values, obtained from the brain images of the same figures as before, 6, 8 and 10, are between 0.0286 and 0.0393, almost half of the obtained ones for the images which illustrate the morbid heterogeneity. This is related to the predominance of higher consistency of brain mass compared to that of microglial histological samples, which is more rarefied.

Figs. 7,9,11 show graphically in 3D the total number of voxels of the respective image, more precisely the gray level, for each pixel, as a function of the number of pixels, both on the ox axis (as the second axis) and on oy axis (as the third axis). As it can be seen from the presented graphs, the gray level (for each pixel) does not exceed the value of 200, having the color scale of three colors, blue, green and yellow on the colored band attached to the right of the image. The small number of gray levels denotes a uniformity of the image and the lack of large gaps, which would have shifted to a spectrum of light colors the gray levels, even to white, equivalent to the lack of matter, to an absolute lacuna. Nevertheless, it is also obvious the uniformity of colors on the whole image (blue color), with a few maximums (picks) of yellow color, discreetly sprinkled on the entire graphic representation. It is remarkable that, in these blue intense zones, darkest color zones coincide with the whiter areas (erosion of matter) in the black and white photographs.

Without us venturing in giving precise diagnoses in the investigations made with the fractal analysis of the examined images, we mention here that the diagnosis of Alzheimer disease is based on specific clinical criteria. However, cranial imaging examination contributes to the diagnosis only by excluding other, potentially treatable, causes such as intracranial masses (such as tumors or subdural hematoma) and normal-pressure hydrocephalus [20,21].

5. Conclusions

In this article a fractal analysis, fractal size and lacunarity, respectively, of a number of three histopathological samples on glial cells, with visible erosions, which have been arranged in distinct classes, in one of the known immuno-pathological models, as in Fig. 1, was done.

The fractal dimension has very high values, over 1.89 and the value of the lacunarity is between 0.050 and 0.079. This is explained by the fact that the stage of the neurological condition is incipient, i.e., by the fact that the dynamic demyelinating multiple sclerosis denudation process is at the beginning, just initiated for the photographed diseased cells.

The same fractal analysis, fractal size and respective lacunarity, of a number of Magnetic Resonance images from three patients, as in Fig. 5, with an annular model, which presented unusual characteristics, was also performed. The fractal dimension in the gray level stages of the studied pictures is above the value of 1.7 and the lacunarity is between the values of 0.0286 and 0.0393.

In 3D graphics, also, the total number of voxels in the respective image, more precisely the gray level as a function of the number of pixels, associated to each pixel within the pictures, has been showed. In fact, we can notice here that these intensively colorized blue areas, more precisely darkest color zones, are identical with the whiter areas (nervous matter erosion), in the black and white photos independently presented.

In termination, we can strongly state that the fractal analysis applied to MRI of cerebral diseases has a major importance in the early detection of brain maladies/disorders and in the monitoring of their progress over time, as such.

Abbreviations

MS, Multiple Sclerosis; CNS, Central Nervous System; MRI, Magnetic Resonance Imaging; $(CV)^2$, Square Coefficient of Variation; OBIA, Object-Based Image Analysis; MAG, Myelin-Associated Glycoprotein; MOG, Myelin-Oligodendrocyte Glycoprotein; KiM1P, Microglia/Macrophages.

Author contributions

VPP and MAP did the conceptualization, VPP conceived the methodology; MVN and VAP produced the software; VPP, MAP and VAP did the validation; VPP, MAP and VAP performed formal analysis; MAP and VAP did the investigation, MAP and VAP took care of the resources; MVN and VAP were responsible with data curation; VPP did the writing—original draft preparation, MAP and VPP did the writing—review and editing, VAP and MVN were responsible with the visualization; VPP was in charge of supervision and project administration. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. VPP is serving as one of the Editorial Board members of this journal. We declare that VPP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GP.

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