Fractal analysis in diagnostic printing in cases of neurodegenerative disorder: Alzheimer type

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Abstract. Alzheimer's disease is a degenerative neurological disorder that comes with the aging process characterized by cognitive, affective and behavioral deficits. A possible method that can support the diagnosis and treatment of Alzheimer's disease is called fractal geometry, given that the brain has fractal structure, therefore, Alzheimer's disease is an observed progressive process of alterations within the groups of topographic voxels, which means that a geometrical fractal analysis can support the diagnosis of the disease. For this purpose, a double blind clinical trial study was designed, calculating the fractal dimension and the lagunarity of magnetic resonance imaging of the cerebral cortex of patients with the neurological report of Alzheimer's disease, implementing the box-counting method or “entropy of kolmogorov”, by means of a software with logarithm FracLac (p=1.029). As a relevant result, a characteristic fractal pattern was evidenced in the images of patients with Alzheimer's disease, which allowed to postulate the mathematical method as a possible analysis to complement the clinical order in the diagnostic assessment.

1. Introduction
Alzheimer's disease (AD) is one of the most important neurological disorders that accompany the aging process, so its prevalence is increasing in parallel with the increase in life expectancy. It is characterized by a great variety of deficits that include cognitive alterations, affective changes and behavioral problems [1]; Its course is progressive, degenerative and disabling [2]. By the year 2030, it is estimated that dementia will be present in 65.7 million of people, and in 115.4 million of human beings by 2050. While in Colombia by 2020 it is expected that 260,000 people over 60 years old will suffer from AD [3].

At the present time the alterations found as a result of the disease are varied, for example, alterations in semantic memory, which do not necessarily occur in the initial stages [4-7], but even in more advanced stages (moderate and severe phases), this has been one of the typical alterations of the ea [8], other alterations found are those mentioned by Muñoz, Iruarriza and Tobal [9] who explored and found alterations in attentional functions, memory, visual-spatial aspects, arithmetic abilities and alterations directly related to genetic functioning in people with AD. Another important study is the one carried out
by Padrón, Menéndez and Llibre [10], who did a review for the identification and isolation of the genes that encode presenilin 1 and 2 (chromosomes 14 and 21, respectively) as well as the detection of mutations, which was one of the achievements of the genetic strategy for the study of AD. This way, the results contributed to the explanation of the high percentage of family history and early onset of the condition.

The genetic factor, despite the direct relationship with the disease, is not the most determining, since as the population ages, the prevalence of dementias becomes greater degenerative. Clinicians must make an accurate diagnosis through a complete evaluation of the patient, including a clinical, neuropsychological, functional assessment, complementary examinations and, evaluation to the family members [11], they also have to assume the enormous challenge of attending to these patients in each of the stages of their evolution and containing their respective family members affected by one of the most feared diseases [12]; considered the epidemic of the century XX.

One of the main factors is associated with AD cardiovascular diseases, which can trigger strokes and high blood pressure, as well as high cholesterol, which inhibits the ability of the blood to eliminate brain proteins, increasing the risk of develop AD, which leads to altering memory, decision making and verbal ability. Also, tau protein has been associated with the onset and progression of Alzheimer’s, generating a toxic spread of the cells of the cerebral cortex affecting attentional, behavioral, planning and thinking processes, which would demonstrate that the amyloid protein is not the only one involved As a direct cause, in the same way, diabetes mellitus type 2 has been linked to AD, where insulin does not work effectively to convert blood sugar into energy, which can damage the brain and contribute to the progression of AD. Oxidative damage has been associated, where free radicals which are unstable molecules resulting from chemical reactions within cells, seek stability by attacking other molecules, damaging cells and neuronal tissues causing AD. On the other hand, immune cells are released from dead cells and other waste products, resulting in inflammation, however, has not yet been confirmed its relationship with the onset of ad. other possible risk factors are traumatic head injuries, low educational level, the reaction of the immune system to a virus [13].

As has been observed, AD is a major neurocognitive disorder (NCD) that is multi-causal and, therefore, presents important drawbacks in order to be accurately diagnosed. According to the National Institute on Aging of Alzheimer's Disease Centers [14], this is a probability diagnosis and it is not surprising that it is qualified as probable Alzheimer's disease, highlighting the need to determine the accuracy of clinical diagnostic methods currently used, being in most cases a diagnosis that remains purely clinical and classified as being delayed [15]. These deficiencies in the diagnostic criteria have a negative impact on the course of the disease and the beginning of treatment of patients with this condition [16], therefore, the majority of Alzheimer's patients receive a late diagnosis [17], and in some cases, it is still very subjective. Currently, mental health professionals perform various psychometric tests to assess cognitive impairment and symptoms associated with this neurocognitive disorder [18], however, on multiple occasions these tests are inconclusive due to the heterogeneity of the symptoms, neurodegeneration process in patients and, the lack of criteria for clinical diagnosis of Alzheimer's dementia sufficiently specific. On the other hand, new neuroimaging techniques have emerged; they have faced the challenge of detecting with high sensitivity and specificity, the prodromal functional alterations that lead to irreversible structural damage [14,15,17], determining activity in the brain and indirectly the topographic involvement of the disease in patients [13].

For this reason, and using the new neuroimaging techniques, a possible method that can support the diagnosis of Alzheimer's disease is the fractal geometry, which is framed in the areas of mathematical analysis, geometry, topology and applied mathematics [19]. The word “fractal” refers to a form that can be irregular, interrupted or fragmented, and remains so at any scale that occurs, being recognized thanks to self-similarity, which means that, “the Everthing” is made up of several copies of itself [20-22].

Regarding biological systems, it has been essential to study the organs that produce changes and detail their chemical and physical behavior; making significant advances in the area of medicine. The irregularities that the organs presented, showed a fractal structure, as they are the conductive fibers of the heart, the networks that form the bronchi, the placenta, the pancreatic ducts, the electrical impulses to the contracting muscles (called a network of His-Purkinje) and human neural networks, which have
a fractal dimension of 2.7 and despite, being found throughout the body, do not occupy more than 5% of it. One of the organs that has been studied with great interest is the brain, whose shape is not smooth but extremely convoluted, with many folds and wrinkles. Also, microscopic examinations have observed that, as the amplification increases, details and small structures are evidently similar to large ones [23].

Therefore, the main objective of this study was to calculate the fractal dimension and the lagunarity factor of the magnetic resonance image of the cerebral cortex of a patient with the neurological report of cognitive impairment: Alzheimer's type, in order to obtain a profile characteristic of the disease, offering evidence of numerical and methodological indicators, that can contribute to the diagnosis of this pathology.

2. Methodology
The present work had a double-blind clinical trial design, with a quantitative approach, a transversal cohort and a descriptive-comparative scope. By analyzing the images of two tomography taken from two brains, one from a healthy patient and another from a patient diagnosed with dementia, see Figure 1, the fractal dimension was calculated using Box Counting and the fractal dimension of Lagunarity.

![Figure 1. (a) Brain image healthy patient (b). Image of a patient with the neurological report of Alzheimer's type cognitive impairment.](image)

2.1. Mathematical method
The fractal analysis was done through software FracLac, who holds an average error probability of $p = 1.029$, being the most effective at the present time to perform this type of analysis, thus, the fractal dimension is a fractional dimension determined by a rational number, widely implemented for the measurement of terrestrial lengths, therefore, the fractal dimension allows the description of the rules that govern an event, given that the vast majority are composed of smaller subcomponents articulated with each other, being determined by self-similarity. To obtain the fractal dimension, different procedures have been implemented, however, the method Box-counting “counting by boxes” or, “Entropy of Kolmogorov”, is the most used technique to calculate the fractal dimension of certain objects that are represented in a plane, thanks to its ease procedure of mathematical calculation and empirical estimation [24].

The method Box-counting is based on the slope of the linear fit between the points and the size of the grid with the relation shown in Equation (1).
\[ D = \frac{\ln(N)}{\ln(k)} \]  

(1)

Where \( N \) is the finite number of subfigures that meets \( K \) congruent with the numerical value \( r = 1/k \), where \( r \) is a factor of contraction. Thus, to have a figure or set \( A \), is covered with regular grid (all squares are equal) of a given length, which are called boxes. With this length, a specific number of boxes is needed to cover the set \( A \), then the length of the boxes is reduced and again the counting of boxes necessary to cover \( A \) is repeated. Repeating this process as the length decreases, it will be necessary more boxes to cover the set \( A \), this process of subdividing and then counting is added to generate a table with these associated data, calculating the limit when the length of the boxes tends to zero of the quotient between the natural logarithm of the number of boxes on the natural logarithm of the reciprocal of length [25]. In order to complement the fractal analysis, the fractal lagunarity was calculated; determining the value of the existing voids in the magnetic resonance images, for this, the average of pixels per box was calculated \((\mu)\). Subsequently, the standard deviation of pixels per box was established \((\sigma)\) and with this the coefficient of variation squared per box was calculated using the Equation (2), then the calculation of the average of all possible \( \lambda \) and an analysis is carried out decreasing in \( \epsilon \), redoing the initial procedure, finally, the average of the averages obtained in all possible \( \lambda \), thus estimating the lagunarity.

\[ (\sigma/\mu)^2 = \lambda \]  

(2)

3. Results and discussion

The main result was a significant difference in the fractal dimension made by means of an analysis Box-counting, in which the magnetic resonance imaging (MRI) of patients who did not have a diagnosis of a greater neurocognitive disorder Alzheimer type, obtained a greater fractal dimension of the cerebral cortex of those MRI of patients diagnosed with AD (Table 1), this result is coherent with previous studies, where observed a decrease of the fractal dimension in celebrated structures analyzed in patients with AD, where progressive morphological alterations have been demonstrated in the cephalic mass of patients with AD [26,27], mainly in the cerebral cortex, since it has been evidenced in the scientific literature a positive correlation between the fractal dimension of the cerebral cortex and the capacities alluded to said region, thus, patients with greater fractal dimension of the cerebral white matter, possessed greater cognitive capacity and intelligence, variables intrinsically related to the appearance and progress of the AD [28].

| Analysis | without-EA | with-EA |
|----------|------------|---------|
| Df-BxC  | 1.565      | 1.464   |
| L        | 0.5997     | 0.9528  |

Table 1. Results of fractal analysis.

Over the last few years, various computational methods in neuroanatomy have been proposed to explore morphological alterations present in patients with suspected neurodegenerative diseases, however, the importance of magnetic resonance has been highlighted, since it aims to analyze the concentration blood oxygen at rest, in this case of the brain, as mentioned above, one of the main ethologist of AD are cardiovascular disorders, such as problems in blood pressure or the accumulation of substances in the bloodstream, Among those that highlights diabetes or high cholesterol levels, which directly alters the oxygen supply to the brain [13]; being a possible triggering factor of this condition. Thus, the analysis of the fractal dimension; an early, specific and determining indicator in the diagnosis and treatment of AD, in the future, The aim is to characterize the values of the fractal dimension with quantitative clinical test values, using the diagnosis and monitoring of patients with dementia, since a positive correlation has been identified between the fractal dimension of the hippocampus and the cerebral cortex with values of clinical tests implemented for the diagnosis of the disease [29].
On the other hand, as regards lagunarity, a marked difference was observed between patients with and without AD diagnosis, however, the numerical event was contrary to the fractal dimension; finding a greater gap in the MRI of patients with AD than in those patients who did not have the diagnosis (Table 1), suggesting a deterioration in the convolutions and cerebral ventricles, decreasing the size of the convolutions, thus, increasing the pressure of the fissures, as well as the diameter of the ventricles, thus, postulating a relevant variable for the characterization of neurodegenerative diseases, mainly in AD, because until now, a histomorphometric investigation has not been carried out to establish a fractal measurement of the cerebral ventricles, which offer values of normality and abnormality [30]. Similarly, given the characteristics of the cephalic mass, as well as MRI, it is very important to take into account possible latent irregularities, since the vast majority of times possible information relevant to clinical decision-making is ignored. It can be weighed by a fractal analysis of lagunarity, since subjective evaluations will no longer be implemented, but instead, measures based on objective and standardized mathematical analyses.

4. Conclusions
The fractal analysis, both dimensions and, lagunarity are measures that can support the detection, diagnosis and evolution of neurodegenerative diseases. However, there is still no great development in this topic, given that, it is still a new field of scientific exploration, therefore, a new research is foreseen in the future, that is expected to achieve a thorough characterization of neurodegenerative diseases, considering various variables associated with the disease as well as the integration and linking of different theoretical and disciplinary perspectives with this process; with the purpose of determine objective parameters that indicate a timely detection, a controlled progress and, give guidelines for an effective treatment.

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