

# The Genesis of Intracranial Aneurysms

## Gênese dos aneurismas intracranianos

Camila Flores<sup>1</sup>

Leonardo C. Welling, M.D.<sup>2</sup>

Eberval G. Figueiredo, M.D. PhD<sup>3</sup>

Manoel J. Teixeira, MD, PhD<sup>4</sup>

### ABSTRACT

**Introduction:** The pathogenesis of intracranial aneurysms remains unclear in spite of its great importance. Besides the "classical" saccular aneurysms, there are other, such as the traumatic, infectious or fusiform ones. This study aims at reviewing the genesis of intracranial aneurysms. **Method:** This review was focused on the Medline/Pubmed data, with the keywords "intracranial" and "aneurysms" from 1990 to 2009. **Conclusions:** The epidemiological studies have identified the endogenous factors such as the elevated arterial blood pressure and the exogenous risk factors (cigarette smoking, heavy alcohol consumption or certain medications) that may lead to the formation, growth and rupture of the intracranial aneurysms. However, its etiology remains unclear and sometimes fatal to those who harbor an intracranial aneurysm. More evidence is needed to establish definitively what factors are responsible for causing intracranial aneurysms.

**Keywords:** intracranial aneurysms, genetics, pathogenesis, epidemiology.

### RESUMO

**Introdução:** A despeito de sua importância, a patogênese dos aneurismas intracranianos permanece obscura. Além dos "clássicos" aneurismas saculares, há os traumáticos, infecciosos e os fusiformes. Este estudo visa revisar a gênese dos aneurismas intracranianos. **Metodologia:** Esta revisão foi baseada no banco de dados da Medline/ PubMed com as palavras "intracranial" e "aneurysms" no período compreendido entre 1990 a 2009. **Conclusões:** Estudos epidemiológicos identificaram fatores endógenos como elevados níveis tensionais e fatores exógenos (tabagismo, etilismo e uso de determinadas medicações) os quais podem levar à formação, crescimento e ruptura dos aneurismas intracranianos. Entretanto, sua etiologia permanece obscura e algumas vezes fatal para aqueles portadores de aneurismas intracranianos. Mais estudos são necessários para estabelecer com precisão quais fatores são responsáveis na gênese dos aneurismas cerebrais.

**Palavras-chave:** aneurismas intracranianos, genética, patogênese, epidemiologia.

### INTRODUCTION

There are many known factors to be related to the intracranial aneurysms growth and rupture, although the pathogenesis involving the formation of a cerebral aneurysm remains unclear<sup>14</sup>.

Some factors are endogenous, such as the elevated arterial blood pressure, an special Circle of Willis anatomy or the possible effect of the hemodynamic factors, particularly originating at vessels bifurcation. Arteriosclerosis and the secondary inflammatory reactions are thought to be elementary preconditions. Other exogenous factors such as cigarette smoking, heavy alcohol consumption or certain known medications which help generate arteriosclerosis and elevated blood pressure have also been found to be related to the occurrence of cerebral aneurysms<sup>10,11,14</sup>.

Furthermore, there has been a long-lasting debate on whether aneurysms might develop as a result of an inborn genetic defect. Patients' first-degree relatives of patients presenting with cerebral aneurysms have a higher risk of having an aneurysm. In addition, the elevated prevalence of cerebral aneurysms in patients suffering from various inherited diseases points to a genetic background in the development of an aneurysm<sup>10,11,14</sup>.

The first record regarding an arterial aneurysm treatment appeared in the Ebers papyrus considering the Egyptian Imhotep (2725 b.C.) to be the first physician to handle it<sup>17</sup>. Then, the real mentor to properly define and describe an arterial aneurysm was Galen of Pergamum in 200 a.C<sup>1</sup>.

Lancisis was responsible for the modern definition of an aneurysm as a weakened artery dilatation in 1728<sup>27</sup>. However, the intracranial aneurysms were definitely described for the first time in the autopsy reports by Morgagni (1761, Padua), Biumi (1765, Milan), and Blane (1800, London)<sup>9</sup>.

The intracranial aneurysm distribution along the different intracranial arteries is unequal, in a way that certain arteries and their segments present aneurysms more often than others, for unclear reasons, but possibly suggesting a different flow relation.

1. Aluno da graduação. Faculdade de Medicina. Universidade Nove de Julho. São Paulo -SP
2. Médico Neurocirurgião. Programa de Pós-Graduação. FMUSP
3. Supervisor Divisão de Clínica Neurocirúrgica. Chefe do Grupo de Neurocirurgia Vascular. HC-FMUSP
4. Diretor de Divisão de Clínica Neurocirúrgica. Professor Titular da Disciplina de Neurocirurgia FMUSP

Recebido em abril de 2010, aceito em junho de 2010

The intracranial aneurysms are classified into two groups based on their morphological features:

- a. Saccular aneurysms: sac-like outpouching of the vessel, usually found at the intracranial arteries bifurcations, comprising 97% of all the intracranial aneurysms;<sup>16</sup>
- b. Fusiform aneurysms (FA): a whole arterial segment dilatation neither with a distinguishable base nor a separate pouch, comprising 3% of all intracranial aneurysms<sup>16</sup>.

The main cause of intracranial aneurysms are believed to be due to <sup>4,16</sup>:

- direct vascular trauma (the traumatic aneurysm);
- bacterial infection (the mycotic aneurysms);
- hemodynamic stress acting on the vessel wall;
- inflammation processes;
- arterial wall remodeling and degeneration;
- extrinsic risk factors (smoking, arterial hypertension, alcohol consumption and genetic predisposition).

The dissecting cerebral aneurysm is probably a result of traumatic injury: its pathophysiology is related to a tear in the intimal layer of the artery wall that may cause a pouch on one side of the artery wall or obstruct the blood flow through it<sup>15</sup>.

Once the saccular aneurysm represents the major part of the aneurysm incidence, this paper aims at reviewing the role played by different factors in the complex issue of the genesis of intracranial aneurysms. However, the fusiform aneurysm pathogenesis will be shortly mentioned too.

## HISTOLOGY OF INTRACRANIAL ANEURYSMS

Three histological layers form a normal intracranial artery<sup>22</sup>:

- the loose connective tissue layer (adventitia);
- the muscular layer in the smooth muscle cells (media);
- the inner layer in the endothelial cells and the smooth muscle cells (intima).

There is also the internal elastic lamina, a very thin layer of elastic fibers, at the border between the media and intimal layers. Once a normal arterial wall is composed of these three separate histological layers, an aneurysm is a dilated segment of a vessel (artery, capillary or vein) without this configuration<sup>7,8</sup>. Basically, four dominant histological wall types have been identified as intracranial aneurysms:

- the endothelialized wall with linearly organized smooth muscle cells (SMCs);
- the thickened wall with disorganized smooth muscle cells;
- the hypocellular wall with fresh or organizing thrombosis;
- extremely thin thrombosis-lined hypocellular wall.

Many aneurysm walls are heterogeneous, constituted by a combination of these four wall types and prevailing in the last two types in ruptured aneurysms. The histological differences between the ruptured and the unruptured intracranial aneurysms suggest that the aneurysm wall is a dynamic structure undergoing constant remodeling<sup>16</sup>. The intracranial aneurysms have a disorganized wall structure, lacking the elastic lamina, the smooth muscle cells (SMCs) and resembling histological intimal thickening (myointimal hyperplasia or neointima) or early atherosclerotic lesions<sup>7,8,12,16,22</sup>.

It is important to emphasize that the extracranial artery wall is composed of an elastic lamina on both limits, the outer and inner limits of the media layer, once the intracranial arteries have only the inner elastic laminae<sup>7,8</sup>. Notwithstanding, the intracranial arteries have a gap in the continuity of the muscular media layer at the bifurcation sites (medial gaps), which have been interpreted as the innate or acquired “defects” in the cerebral artery wall that would have less tensile strength and therefore some predisposition to an aneurysm formation at the bifurcation sites<sup>7,8</sup>.

On the other hand, it remains unclear how the epidemiological SAH risk factors (smoking, hypertension, female gender, prior SAH, age) affect the aneurysm wall and lead to the cell loss, matrix degeneration, and an eventual rupture. Some studies have reported that aneurysm wall rupture is related to apoptosis and matrix degeneration<sup>6,7,8</sup>.

Other important factor is the increased proteolytic activity and the metalloproteinases (MMPs) expressions associated with the arterial wall remodeling in myointimal or atherosclerotic lesions<sup>7,8</sup>. The MMP-9 inhibition and the MMP-12 activity seem to protect the atherosclerotic arterial media layer from the transmedial elastin degradation and aneurysmatic enlargement (the ectasia)<sup>7,8</sup>.

The apoptotic event is significant and intriguing to consider for the intracranial aneurysm studies. It has been seen that many aneurysm cell walls are undergoing the programmed cell death (apoptosis) when a normal arterial wall practically has extremely few or no apoptotic cells<sup>7,8,21</sup>.

## SACCULAR CEREBRAL ARTERY ANEURYSMS (SCAAs)

The saccular or berry aneurysm is the most common type of cerebral aneurysm, comprising 90% of cases. The SCAA is thought to have different rupture risks depending on its location in the Circle of Willis and the cerebral vascular tree<sup>7,8</sup>. A large meta-analysis of the ruptured saccular cerebral aneurysm (ISUIA) reported that those aneurysms arising from the posterior circulation as well as those arising from the posterior communicating artery have an increased rupture risk when compared to those aneurysms arising from the anterior circulation<sup>24</sup>.

It seems that the rupture risk is higher for saccular aneurysms at AcomA or ACA, which represent the most common site of rupture (40%). This suggests that the AcomA aneurysms are more likely to rupture than the middle cerebral artery bifurcation ones (20-30%)<sup>7,8,26</sup>. Some authors mention that the risk of an aneurysm to rupture increases with over 10 mm size. On the other hand, there are very low rupture risks for those aneurysms smaller than 7 mm (0,05%) compared to aneurysms larger than 7 mm (1%), considering that those patients did not have a previous SAH<sup>10,26</sup>.

## ORIGIN OF SACCULAR ANEURYSMS

It is often believed that the saccular aneurysms are congenital lesions as the wall degeneration is barely identified macroscopically, but they can be found in patients with anatomical variations in the Circle of Willis<sup>7,8,10,11</sup>.

It must be mentioned that saccular aneurysms seem to be acquired lesions due to the exposure to risk factors, congenital defects and malformations that alter the cerebral circulation hemodynamics and can predispose to the saccular aneurysm formation<sup>7,8,10,11</sup>.

## HEMODYNAMIC STRESS

Some studies report that the saccular aneurysms can be induced by an increased hemodynamic stress, or an imbalance between hemodynamic stress and cerebral artery wall strength. The cerebral vasculature is under high hemodynamic stress even in physiological conditions, since it receives approxima-

tely 15% of the cardiac output to meet the high brain oxygen consumption (approximately 20% of total body oxygen consumption)<sup>6,7,8,13</sup>.

The knowledge of such mechanisms remains unclear so far, although it is believed that arterial hypertension induces the de-endothelization, followed by destructive changes in the inner elastic lamina at the cerebral artery bifurcations. This means that hemodynamic stress probably leads to the arterial wall degeneration via increased proteolytic activity<sup>6,7,8</sup>.

Arteries adapt to the increased shear stress and the increased hemodynamic pressure by the hypertrophy of the medial layer, adventitial fibrosis, and myointimal hyperplasia<sup>7,8</sup>. The myointimal hyperplasia pads are often found near the cerebral artery bifurcations and close to the bifurcation where saccular aneurysms form. It seems that myointimal hyperplasia also contributes to the weakening of the inner elastic lamina in the bifurcation wall<sup>7,8</sup>.

## INFECTION AND INFLAMMATION

In addition to those produced by hemodynamic stress, some saccular aneurysms are caused by cerebral artery wall infection. These aneurysms are called mycotic, and represent only 2-6% of all saccular aneurysms. However, it has been proposed that the inflammation or activation in the inflammatory system might also be involved in the formation of saccular aneurysms in general, based on the finding that macrophages, T-cells, B-cells, antibodies and complement activation are found in the unruptured SCAA walls<sup>3,4,7,8</sup>.

Inflammation increases the proteolytic activity and causes necrosis and apoptosis. These events damage the arterial wall, leading to tensile strength loss, and predisposing to the enlargement of the aneurysm<sup>7,8</sup>.

## MONOGENIC DISEASE ASSOCIATED

The most common monogenic disease associated with saccular aneurysms is the autosomal polycystic kidney disease (APCKD), which is found in approximately 0.3% of the patients<sup>23</sup>. Other frequent monogenic diseases that have traditionally been associated with the SCAAs include<sup>23</sup>:

- a. Ehler-Danhlos syndrome type IV (mutation in collagen III);
- b. Marfan syndrome (mutation in fibrillin-1, a component of the elastic lamina);

- c. Fibromuscular dysplasia (excessive myointimal hyperplasia formation, unknown mutations)
- d. Pseudoxanthoma elasticum which did not seem to really associate with SCAAs in a recent patient series.

In addition to the monogenic diseases, approximately 10% of SAH patients have a familial background. The exact inheritance pattern and penetrance of familial SCAAs in different populations still have not been established. The Finnish familial saccular aneurysms have been associated with the genome wide linkage analysis to a 6.6 cM region of the chromosome 19q13.3, but the Finnish aneurysm gene still remains to be found<sup>7,8,25</sup>.

Several genome wide linkage analyses of familial SCAAs have revealed associations with the 7q11 region, the 7q22 region, the 17 cen, 19q13, and Xp22 regions and a weaker association with the 5q22-31 region in the Japanese population. The Japanese aneurysm gene has not been found yet. The 7q11 locus association with the SCAAs has been replicated by the white population, but was not replicated by all Japanese studies<sup>19,25</sup>.

The Mendelian autosomal dominant form of familial SCAAs has been linked with the 1p34.3-p36.13 locus in the North American population<sup>18</sup>. Although the genetic defects that may cause familial saccular aneurysms remain unknown, the known SAH risk factors, the known monogenic disorders and the genetic polymorphisms are assumed to be associated with the saccular aneurysms. In this context, all the genetic defects that predispose to saccular aneurysms may lead to increased hemodynamic stress in the cerebral artery bifurcations; also, to the structural weakness in the arterial wall, to modification of the repair and adaptation mechanisms in the arterial wall and to modification of the systemic inflammatory response or adaptive immunity in the artery wall.

Moreover, it can be deduced that the acquired environmental factors (e.g. smoking, hypertension, cerebral artery wall infections) may lead to similar consequences increasing the risk of aneurysm formation and rupture. These factors should be avoided in patients with a SAH risk, especially in those with a genetic predisposition<sup>7,8</sup>.

## IMMUNE RESPONSE

It has already been proposed that the saccular aneurysm wall degeneration may be caused by an immune reaction against the SCAA wall components [7,8]. This hypothesis is supported by the observations that inflammatory cell infiltration is increased in the ruptured aneurysm walls and that the pro-apoptotic in-

flammatory cytokine and the TNF-alpha are synthesized in the ruptured SCAA walls<sup>3</sup>. The presence of macrophages, T-cells, B-cells, IgM and Ig-G-antibodies and the activated complement in the SCAA wall confirms an ongoing inflammatory reaction mediated by the innate and adaptive immune system<sup>7,8</sup>.

## REPAIR MECHANISMS

Despite the aneurysm wall is constantly subject to the hemodynamic stress, many saccular aneurysms never rupture, suggesting that its wall has some adaptation and repair mechanisms that are in balance with hemodynamic and other stress factors<sup>7,8</sup>.

The adaptation mechanism of the normal arteries to the hemodynamic stress is myointimal hyperplasia. The saccular aneurysm walls histopathologically resemble the myointimal hyperplasia. Due to the histopathological resemblance between the unruptured SCAA wall and the myointimal hyperplasia, it likely seems that the SCAA wall reacts to the increased hemodynamic stress via an increased cell proliferation and matrix synthesis as myointimal hyperplasia elsewhere<sup>24</sup>.

Other disease entities suggest that the protease-antiprotease imbalances contribute to the somatic vessel wall degradation and aneurysm formation. The detection of similar imbalances in selected patients may identify a predisposition to the cerebral aneurysm formation. Baker et al<sup>2</sup> reported a study of serum concentrations of elastase and alpha-1-antitrypsin (AAT), important proteolytic and antiproteolytic enzymes, which were measured in a series of 19 patients with unruptured aneurysms, 41 patients with ruptured aneurysms and 27 age-matched operative and nonoperative controls. The elastase AAT ratio was nearly twice as high in patients with unruptured aneurysms as the ones in operative controls (0.527 +/- 0.1 versus 0.285 +/- 0.06; P < 0.04). Elastase:AAT ratios in patients with ruptured aneurysms (subarachnoid hemorrhage < 48 h) were roughly twice those ones in controls (0.582 +/- 0.095; P < 0.01)<sup>2</sup>.

## FUSIFORM ANEURYSMS

Fusiform aneurysms constitute dilatations in the whole vessel wall for a short distance. They are rare, representing 3-13% of the intracranial aneurysms (20) and basically found in the anterior circulation in 77% of the patients while in the posterior circulation in 23% of the patients. It was found out that among

69% of the aneurysms originated proximally to the MCA (middle cerebral artery) genu (M1 segment), 21% were insular (M2 segment) and 10% were distal (M3 or M4 branches). The MCA was also the most frequent site of origin, followed by the internal carotid and anterior cerebral arteries<sup>20</sup>.

The age and sex distribution of patients with fusiform aneurysms differ from those with the saccular ones. The patients' mean age is 45 years-old and the male/female ratio is 1.4:1<sup>20</sup>. This contrasts with the patients with saccular aneurysms, as spontaneous fusiform aneurysms are more often found in younger and male patients<sup>5,20</sup>.

The possible causes of fusiform aneurysms are vessel dissection, atherosclerosis, collagen disease or unknown factors<sup>20</sup>. There is an association with other diseases such as von Recklinghausen's disease, fibromuscular dysplasia, systemic lupus erythematosus and various collagen-associated vascular diseases<sup>20</sup>.

The initial event in the formation of the atherosclerotic fusiform aneurysms is thought to be intimal lipid deposition, with disruption of the internal elastic membrane and infiltration of the muscular wall. Intramural hemorrhage and atheroma rupture may lead to the transmural extension of the thrombus and thickening of the intima, with creation of the fusiform shape of the aneurysm<sup>5, 20</sup>.

## CONCLUSIONS

Epidemiological studies have identified endogenous factors such as elevated arterial blood pressure and exogenous risk factors (cigarette smoking, heavy alcohol consumption or certain medications) that may lead to the formation, growth and rupture of the intracranial aneurysms. However, its etiology remains unclear and often fatal to those who carry an intracranial aneurysm. More evidence is needed to establish definitively what factors are responsible for causing intracranial aneurysms.

## REFERENCES

1. Apuzzo ML. The legacy of Galen of Pergamon. *Neurosurgery* 2000;47:545.
2. Baker CJ, Fiore A, Connolly ES Jr, Baker KZ, Solomon RA. Serum elastase and alpha-1-antitrypsin levels in patients with ruptured and unruptured cerebral aneurysms. *Neurosurgery* 1995;37(1):56-61; discussion 61-2.
3. Chyatte D, Bruno G, Desai S, Todor DR. Inflammation and intracranial aneurysms. *Neurosurgery* 1999; 45:1137-46; discussion 1146-7.
4. Clare CE, Barrow DL. Infectious intracranial aneurysms. *Neurosurg Clin N Am* 1992; 3(3):551-66.
5. Day AL, Gaposchkin CG, Yu CJ, Rivet DJ, Dacey RG Jr. Spontaneous fusiform middle cerebral artery aneurysms: characteristics and a proposed mechanism of formation. *J Neurosurg.* 2003; 99:228-40
6. Foutarakis GN, Yonas H, Scialabasi RJ. Saccular aneurysm formation in curved and bifurcating arteries. *AJNR Am J Neuroradiol* 1999; 20:1309-17
7. Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, et al. Growth factor receptor expression and remodeling of saccular cerebral artery aneurysm walls: implications for biological therapy preventing rupture. *Neurosurgery* 2006; 58(3): 534-41
8. Frösen J, Piippo A, Paetau A, Kangasniemi M, Niemelä M, Hernesniemi J, et al. Remodeling of saccular cerebral artery aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. *Stroke* 2004; 35(10): 2287-93.
9. Hernesniemi J, Dashti R, Mateo O, Cancela P, Karatas A, Niemela M. Historical landmarks in vascular Neurosurgery "On July 10th 2006, at the 70th Anniversary of the Department of Neurosurgery of Zürich Medical School". *Acta Neurochir Suppl*; 2008 103:131-37.
10. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. *J Neurosurgery* 2000; 93:379-87.
11. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke* 2001; 32: 485-91.
12. Kataoka K, Taneda M, Asai T, Kinoshita A, Ito M, Kuroda R. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. *Stroke* 1999; 30(7):1396-401.
13. Kim SC, Singh M, Huang J, Prestigiacomo CJ, Winfre CJ, Solomon RA, et al. Matrix metalloproteinase-9 in cerebral aneurysms. *Neurosurgery* 1997; 41: 642-66; discussion 666-7.
14. Krex D, Schackert H. K, Schackert G. Genesis of Cerebral Aneurysms - An Update. *Acta Neurochir (Wien)*. 2001; 143: 429-9
15. Krishnakumar K, Menon G, Kesavadas C, Nair S, Rao BR, Easwer HV. Dissecting intracranial aneurysms presenting as subarachnoid haemorrhage: report of two cases and review of literature. *Br J Neurosurg* 2008; 22(6): 801-4.
16. Lehecka M, Dashti R, Lehto H, Kivisaari R, Niemelä M, Hernesniemi J. Distal anterior cerebral artery aneurysms. *Acta Neurochir Suppl* 2010; 107:15-26
17. Lippi D. An aneurysm in the Papyrus of Ebers. *Med Secoli* 1990; 2(1):1-4.
18. Nahed BV, Seker A, Guclu B, Ozturk AK, Finberg K, Hawkins AA, et al. Mapping a mendelian form of intracranial aneurysm to 1p34.3-p36.13. *Am J Hum Genet* 2005; 76: 172-9.

19. Onda H, Kasuya H, Yoneyama T, Takakura K, Hori T, Takeda J, et al. Genome wide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. *Am J Hum Genet* 2001; 69: 804-19.
20. Park SH, Yim MB, Lee CY, Kim E, Son EI. Intracranial Fusiform Aneurysms : It's Pathogenesis, Clinical Characteristics and Managements. *J Korean Neurosurg Soc.* 2008;44:116-23
21. Pentimalli L, Modesti A, Vignati A, Marchese E, Albanese A, Di Rocco F, et al. Role of apoptosis in intracranial aneurysm rupture. *J Neurosurg* 2004; 101:1018-25
22. Ross MH, Romrell, LJ, Kaye, GI. *Histology: a text and atlas* (3 ed) Williams & Wilkins, Baltimore. USA, 1995.
23. Schievink WI. Genetics of intracranial aneurysms. *Neurosurgery* 1997; 40:651-62; discussion 662-3
24. The International Study of Unruptured Intracranial Aneurysms Investigators. ISUIA. Unruptured intracranial aneurysms- risk of rupture and risks of surgical intervention. International Study of Unruptured Intracranial Aneurysms Investigators. *N Engl J Med* 1998; 339: 1725-33
25. Van der Voet M, Olson JM, Kuivaniemi H, Dudek DM, Skunca M, Ronkainen A, et al. Intracranial aneurysms in Finnish families: confirmation of linkage and refinement of the interval to chromosome 19q13.3. *Am J Hum Genet* 2004; 74:564-71.
26. Weir B, Disney L, Karrison T. Sizes of ruptured and unruptured aneurysms in relation to their sites and ages of patients. *J Neurosurgery* 2002; 96:64-70.
27. Wolpert SM. On the radiologic diagnosis of cerebral aneurysms with plain films and cerebral angiography: a historical survey. *AJNR Am Neuroradiology* 1995;16:181-4.

## CORRESPONDING AUTHOR

*Eberval G Figueiredo, MD, PhD*  
*Rua Enéas de Carvalho Aguiar, 255*  
*Instituto Central – Divisão de Neurocirurgia*  
*HCFMUSP – São Paulo – SP - e-mail:*  
*ebgadelha@yahoo.com*