Leão's cortical spreading depression

From experimental "artifact" to physiological principle

H.A.G. Teive, MD, PhD; P.A. Kowacs, MD; P. Maranhão Filho, MD, PhD; E.J. Piovesan, MD; and L.C. Werneck, MD, PhD

Abstract—Cortical spreading depression was described in 1943 by Aristides Leão, a Brazilian neurophysiologist. Initially considered to be a mysterious event as it was discovered serendipitously, its nature has become progressively better known. Cortical spreading depression is now accepted as the mechanism underlying migraine aura and has became known as either Leão's spreading depression or cortical spreading depression. Recent studies have suggested a role for Leão's cortical spreading depression in the pathogenesis and symptomatology of neurologic disorders such as transient global amnesia, head injury, and cerebrovascular diseases.

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Leão's cortical spreading depression (LCSD) was described in 1943 by Aristides Leão, a Brazilian neurophysiologist, during his PhD fellowship in physiology at Harvard University. In 1944, Leão published a seminal paper entitled "Spreading depression of activity in the cerebral cortex," subsequently known internationally as Leão's spreading depression.[1]

Several years later, evidence of the role played by LCSD in the mechanism of migraine aura was reinforced, and recent studies have emphasized the role of LCSD in the pathogenesis and symptomatology of other conditions such as transient global amnesia, head injury, and cerebrovascular diseases.[2]

The aim of this study is to report the original description of LCSD, to analyze the evolution of the concepts involving this phenomenon, and to highlight its role in the mechanism of several neurologic disorders.

The protagonist. Professor Aristides Azevedo Pacheco Leão (figure 1) was born on August 3, 1914, in Rio de Janeiro, Brazil.[3] He attended high school at the Colégio Andrews, in Rio de Janeiro, and later went on to medical school at the Faculdade Paulista de Medicina, in São Paulo. He had to leave medical school in the second year because of health problems, and moved to Correas in the state of Minas Gerais to recover from his illness. His recovery took 2 years and prevented him from graduating. When he was finally allowed to leave the hospital, in 1940, he was 26 years old.[3] He persuaded his family to support a study trip to North America, where he was accepted at Harvard University, in Cambridge, MA, to study Medical Sciences (Physiology). He took an MA degree in 1942, and was granted an Austin Teaching Fellowship in the Department of Physiology (1942–1943). In 1943 he was awarded a PhD after defending the thesis that made him famous in the scientific world. In 1944 he became a Research Fellow of the Department of Anatomy at the Harvard Medical School, Boston, MA.[3,4] At the age of 32, already back in Rio, he joined the Faculdade Nacional de Medicina of Universidade Federal do Rio de Janeiro as a Specialized Technician in the chair of Biologic Physics, and as a teacher of Comparative Anatomic Physiology at the Faculdade de Fisiologia (College of Physiology) in the same university.[3]

Leão subsequently became in turn Professor, Emeritus Professor, Director, and Head of the Neurobiology Department, in the "Carlos Chagas Filho" Institute of Biophysics at the Universidade Federal do Rio de Janeiro, Brazil. He was also Professor of Physiology and Anatomy (Zoology Department) and Physiology (Biomedical Department) at the Universidade do Brazil.[3]

For a number of years he was President of the Brazilian Academy of Sciences and Visiting Scientist at the Neurophysiology Laboratory of the National Institute of Mental Health, NIH, Bethesda, MD. He was a member of several Brazilian and International Scientific Committees.[3] He died on December 14, 1993, in Rio de Janeiro.

From the Neurology Service, Internal Medicine Department, Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil.

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Address correspondence and reprint requests to Dr. Hélio A.G. Teive, Rua General Carneiro 1103/102, Centro, 80060-150, Curitiba, Pr, Brazil; e-mail: hagteive@mps.com.br

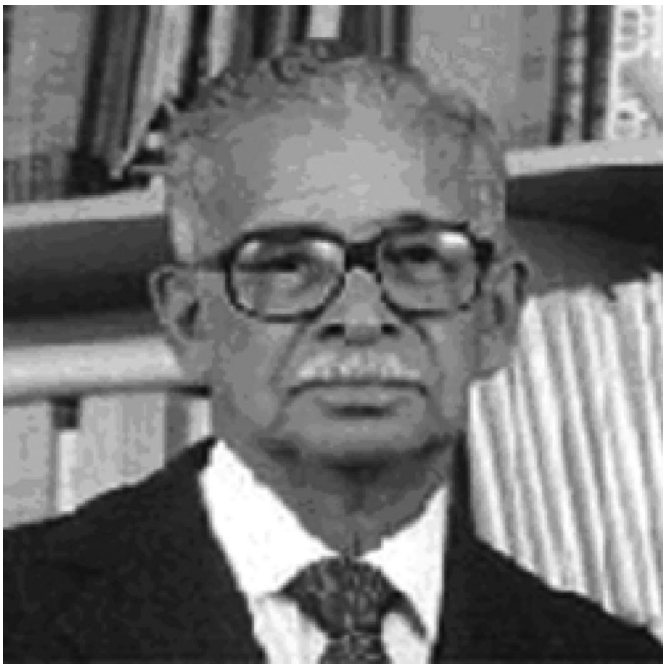

Figure 1. Professor Aristides A.P. Leão.

A mysterious, serendipitous experimental event. In the early 1940s, while a PhD Fellow, Professor Aristides Leão started his research on "experimental epilepsy" under the supervision of Professor Hallowell Davis and Dr. Arturo Rosenblueth at the Department of Physiology of the Harvard Medical School.[4] Dr. Leão and Dr. Rosenblueth were studying electrical activity in the brains of rabbits under general anesthesia. The phenomenon they wished to study was called cortical epilepsy, described by Dr. Davis as ". . . a burst of activity which could be initiated by direct stimulation of the cortical surface and which spread for some distance from the point of stimulation. . . ."[4]

Professor Leão started the experiment, and following the electrical stimulation there was a most unexpected and contradictory result: "the activity at the nearest pair of recording electrodes did not increase, but ceased almost entirely" (figure 2). Dr. Davis was called in for consultation and said: ". . . nothing resembles a new phenomenon as much as a good artifact."[4]

In summary, the response consists of a marked, enduring reduction of electrical activity, a reduction which appears first at the region that has been stimulated, and spreads out from there in all directions, involving successively more and more distant parts of the cerebral cortex. The rate of spread is slow. In rabbits under dial narcosis, a response that started near the frontal pole may take more than 5 minutes to reach the ipsilateral occipital pole. Recovery to the initial pattern of spontaneous electrical activity takes 5 to 10 minutes, or even more, varying from region to region (figure 3).[1]

After being described for the first time, the phenomenon proved to be reasonably reproducible. In 1944, Leão published a seminal article derived from his PhD thesis submitted in October 1943 as a partial requirement for obtaining his degree from Harvard University. The article was entitled "Spreading depression of activity in the cerebral cortex," and became internationally known. The phenomenon was subsequently called Leão's spreading depression.[1] In this article Leão stressed that "this study originated from an attempt to secure more data for the understanding of the cortical electrogram which occurs in experimental epilepsy," and of the conditions in which it is brought forth by electrical stimulation. Early in the development of the study, an interesting response, elicited by electrical stimulation, was noticed in the cortex of rabbits. The distinctive feature of this response was a marked, enduring reduction of the "spontaneous electrical activity of the cortex. We have endeavored to experimentally define some of the characteristics of this response."[1] In the summary of his original article, Leão commented that ". . . specific activity, different from the spontaneous, often develops during the period of depression of a region. The most common type of this activity is composed of large, slow, localized potential waves, during which one electrode becomes negative in relation to others 1 to 3 mm distant," and ". . . the depression and "tonic-clonic" activity of experimental cortical epilepsy seem to be closely related phenomena. The spread of tonic-clonic responses is probably mediated by the same cortical elements which are involved in the spread of depression. The two processes are mainly or exclusively cortical, i.e., they do not require a contribution from sub-cortical centers."[1]

Leão demonstrated in rabbits under dial narcosis that vasodilation with increased blood flow in the pial vessels over the cerebral hemispheres occurred concomitantly with the cortical spreading depression after stimulation of the cerebral cortex.[5]

In 1945, Leão and Morrison studied the propagation of cortical spreading depression and suggested for the first time that this phenomenon could be involved in the pathophysiology of migraine, since the slow march of scotomata in the visual or somatic sensory areas was suggestively similar to LCSD.[6] It should be stressed that Leão and Morrison were at that time unaware of Lashley's article on migraine aura published in 1941, in which he described the scintillating scotomatas of his own migraine with aura and determined that it moved at the speed of 3 mm/minute across the visual cortex.[7]

A relationship between Lashley's findings and LCSD was stressed by Milner (1958) and Basser (1969), and was confirmed by other researchers including Garner-Medwin (1981) and Lauritzen (1994).[8-11]

Further observations by Professor Leão on spreading depression in the cerebral cortex were published in 1947 and 1951, and this phenomenon was further described in other brain areas, such as the hip-

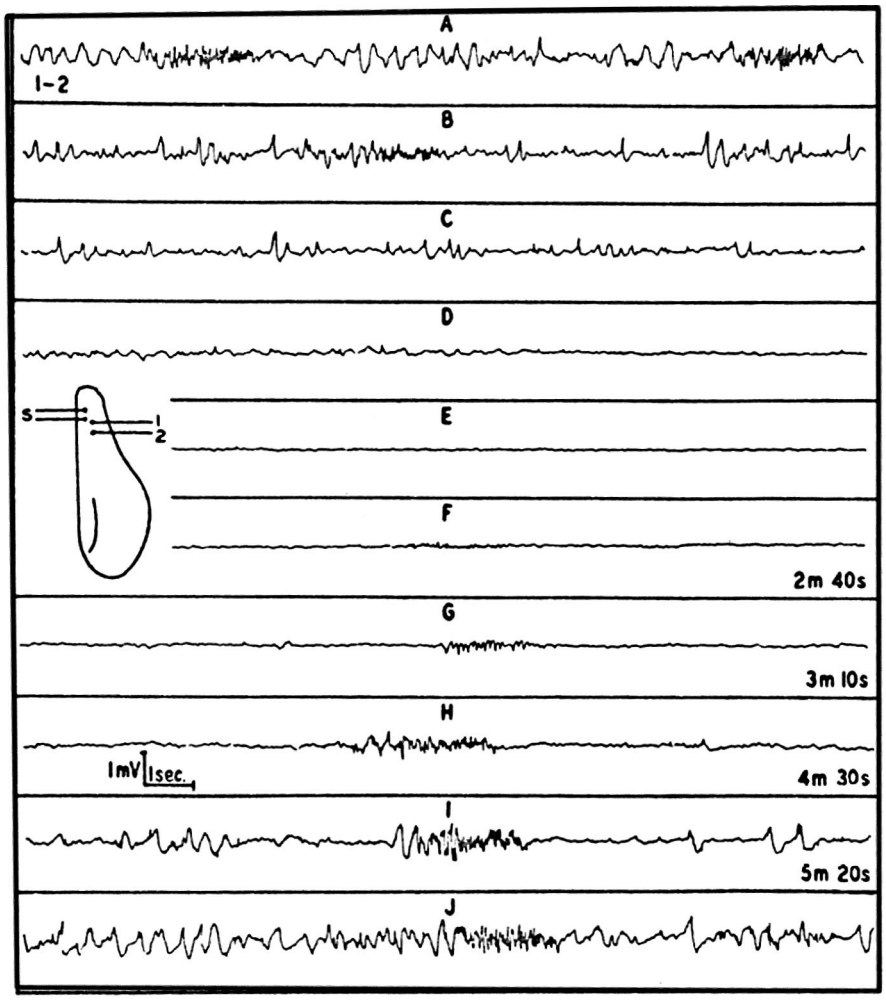

Figure 2. Depression of the spontaneous electrical activity at the region stimulated. A, Before stimulation; B to I, continuous records after the end of stimulation; J, complete recovery (extracted, with permission, from reference 1).

pocampal formation, the striatum, the cerebellum, and the retina of different animals, including chicks, monkeys, rats, frogs, and cats.[12-14] He continued his line of research, and in a few years discovered all the major features of CSD. Leão's studies suggested five major characteristics of CSD, which are, in his own words, that "1) CSD occurs only in certain conditions that render the tissue susceptible to it; 2) the speed of the spread is in the order of 3 mm/minute, and the profound depression lasts for 1–3 minutes at all

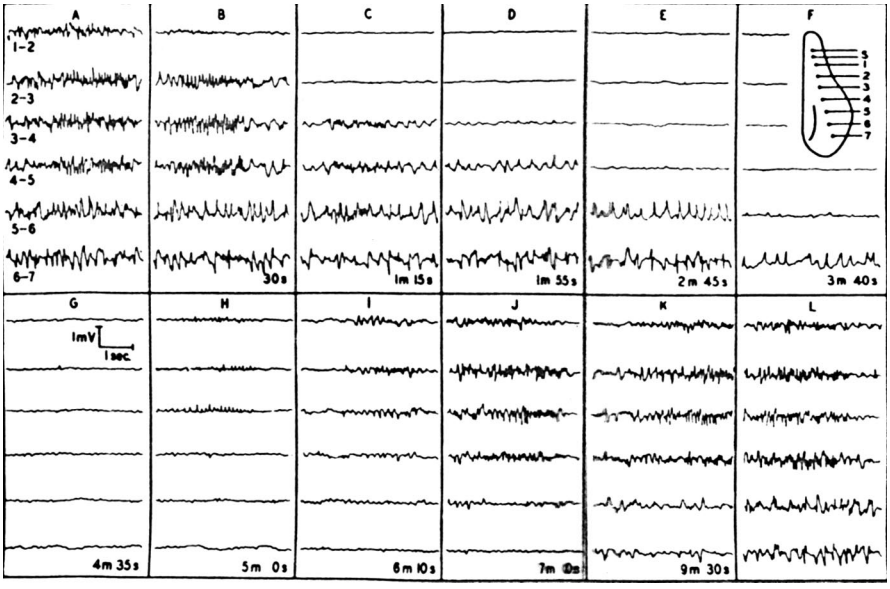

Figure 3. Gradual spread of depression. A, Before stimulation; B to K, records; L, recovery (extracted, with permission, from reference 1).

sites; 3) the spread is self-sustained; 4) although all intrinsic and evoked neuronal activity is depressed, abnormal activity may occur locally in the course of CSD; 5) CSD is followed by an absolute refractory period of at least 1 minute at all sites."[14]

In the words of Professor Jean Bures and colleagues, Aristides Leão remained the acknowledged head of the invisible college he had founded. Rio became a Mecca for CSD research, visited by scientists from the United States, France, England, Japan, Germany, Czechoslovakia, Denmark, and Russia.[15]

A fashionable hypothesis for some neurologic disorders. Current studies in LCSD confirm that this phenomenon plays an important role in some neurologic disorders, including migraine, transient global amnesia, cerebrovascular disorders, and head injury.[2,16-19] Indeed, several studies carried out in recent years have confirmed that the aura phase of migraine is associated with a reduction in cerebral blood flow.[20-23]

In 1990, Olesen et al. characterized the timing and topography of cerebral blood flow, aura, and headache during migraine attacks. This group described a "spreading oligemia" that occurs at 2 to 3 mm/minute, corresponding to the rate of progression of Lashley's scotomatas and the cortical spreading depression phenomenon described by Leão.[23]

Despite the aforementioned evidence, the role of LCSD in migraine was disputed by some, as the phenomenon of LCSD was not consistently reproduced in the human brain. Nowadays, there is no doubt that the migraine aura is caused by LCSD or a neurophysiologic phenomenon akin to LCSD, a wave of short lasting neuronal excitation, followed by prolonged depression of cortical neuronal activity.[2,16,24,25]

LCSD has also been observed in magnetoencephalographic fields from patients with spontaneous and induced migraine aura and in diffusion-weighted MRI (DWI).[26,27] Bradley et al. demonstrated the feasibility of using DWI to evaluate the therapeutic effects of spreading cortical depolarization and depression of electroencephalographic activity.[27]

Transient global amnesia (TGA) remains a puzzle from a pathogenic point of view. In recent years, however, several studies have emphasized the relationship between LCSD and TGA. TGA is thought to be related to disturbances of the brain's physiology that cause transient alteration in brain metabolism, such as LCSD.[2,18,28]

The relationship between LCSD and cerebrovascular disorders has recently been the subject of speculation in the literature.[2,29] An article published in 2003 by Ottori et al. described LCSD as causing a long-lasting decrease in cerebral blood flow and inducing tolerance to permanent focal ischemia in rat brain.[17] Strong et al. evaluated 14 patients undergoing neurosurgery after head injury or intracranial hemorrhage, using electrocorticographic (ECoG) electrodes near the foci of damaged cortical tissue. They observed a transient depression of ECoG amplitude in 8 of the 14 patients, and concluded that LCSD or a similar event occurs in the injured human brain.[19]

Other studies have suggested a link between LCSD and head trauma.[2].

Conclusions. Cortical spreading depression was discovered in 1943 by Aristides Leão while studying cortical epilepsy, and for several years it was considered a rather unexplained, serendipitous, experimental event. Several studies have confirmed the relevance of LCSD in the mechanism of several neurologic disorders such as migraine, transient global amnesia, cerebrovascular disease, and head injury.

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References

1. Leão AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944;7:359–390.
2. Gorji A. Spreading depression: a review of the clinical relevance. Brain Res Rev 2001;38:33–60.
3. Brazilian Academy of Sciences, 2003. Available at: http://www.abc.org.br/historia/aristides_leao.html.
4. Davis H. Introductory words. In: Current views on Leão's spreading depression. Anais da Academia Brasileira de Ciências 1984;56:369–370.
5. Leão AAP. Pial circulation and spreading depression of activity in the cerebral cortex. J Neurophysiol 1944;7:391–396.
6. Leão AAP, Morison RS. Propagation of spreading cortical depression. J Neurophysiol 1945;8:33–46.
7. Lashley KS. Patterns of cerebral integration indicated by the scotomas of migraine. Arch Neurol Psychiatry 1941;331–339.
8. Milner PM. Note on a possible correspondence between scotomas of migraine and spreading depression of Leão. Electroencephalogr Clin Neurophysiol 1958;10:705.
9. Basser LS. The relation of migraine and epilepsy. Brain 1969;92:285–300.
10. Gardner-Medwin AR. Possible roles of vertebrae neuroglia in potassium dynamics, spreading depression and migraine. J Exp Biol 1981;95:111–127.
11. Lauritzen M. Pathophysiology of the migraine aura: the spreading depression theory. Brain 1994;117:199–210.
12. Leão AAP. Further observations on the spreading depression of activity in the cerebral cortex. J Neurophysiol 1947;10:409–414.
13. Leão AAP. The slow voltage variation of cortical spreading depression of activity. Electroencephalogr Clin Neurophysiol 1951;3:315–321.
14. Leão AAP. On the inferred relationship of migraine and spreading depression. In: F. Clifford Rose, ed. Advances in headache research. London: John Libbey & Co., 1987;19–24.
15. Burés J, Buresová O, Krivanek J. The mechanisms and applications of Leão's spreading depression of electroencephalographic activity. New York: Academic Press, 1974.
16. Lauritzen M. Cortical spreading depression in migraine. Cephalalgia 2001;21:757–760.
17. Otori T, Greenberg JH, Welsh FA. Cortical spreading depression causes a long-lasting decrease in cerebral blood flow and induces tolerance to permanent focal ischemia in rat brain. J Cereb Blood Flow Metab 2003;23:43–50.
18. Pantoni L, Lamassa M, Inzitari D. Transient global amnesia: a review emphasizing pathogenic aspects. Acta Neurol Scand 2000;102:275–283.
19. Strong AJ, Fabricius M, Boutelle MG, et al. Spreading and synchronous depression of cortical activity in acutely injured human brain. Stroke 2002;33:2738–2743.
20. Olesen J, Larsen B, Lauritzen M. Focal hyperemia followed by spreading oligemia and impaired activation of rCBF in classic migraine. Ann Neurol 1981;9:344–352.
21. Lauritzen M, Skyhoj-Olsen T, Lassen NA, Paulson OB. The changes of regional cerebral blood flow during the course of classical migraine attacks. Ann Neurol 1983;13:633–641.
22. Lauritzen M, Olesen J. Regional cerebral blood flow during migraine attacks by Xenon-133 inhalation and emission tomography. Brain 1984;107:447–451.
23. Olesen J, Friberg L, Skyhoj-Olsen T, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol 1990;28:791–798.
24. Ebersberger A, Schaible HG, Averback B, Richter F. Is there a correla-

tion between spreading depression, neurogenic inflammation, and nociception that might cause migraine headache? Ann Neurol 2001;49:7–13.
25. Spierings EL. Pathogenesis of the migraine attack. Clin J Pain 2003;19:255–262.
26. Bowyer SM, Aurora KS, Moran JE, Tepley N, Welch KM. Magnetoencephalographic fields from patients with spontaneous and induced migraine aura. Ann Neurol 2001;50:582–587.
27. Bradley DP, Smith MI, Netsiri C, et al. Diffusion-weighted MRI used to detect in vivo modulation of cortical spreading depression: comparison of sumatriptan and tonabersat. Exp Neurol 2001;172:342–353.
28. Jovin TG, Vitti RA, McCluskey LF. Evolution of temporal lobe hypoperfusion in transient global amnesia: a serial single photon emission computed tomography study. J Neuroimaging 2000;10:238–241.
29. Petzold GC, Einhaupl KM, Dirnagl U, Dreier JP. Ischemia triggered by spreading neuronal activation is induced by endothelin-1 and hemoglobin in the subarachnoid space. Ann Neurol 2003;54:591–58.