Thalamic alexia with agraphia

Fábio Henrique de Gobbi Porto,1 Maria Isabel d’Ávila Freitas,1 Maira Okada de Oliveira,1 Leandro Tavares Lucato,2 Marco Orsini,3 Sara Lúcia Silveira de Menezes,4 Regina Míksian Magaídi,5 Cláudia Sellitto Porto,1 Sonia Maria Dozzi Brucki,1 Ricardo Nitiri1

1Behavioral and Cognitive Neurology Unit, Department of Neurology and Cognitive Disorders Reference Center (CEREDIC); 2Department of Radiology, Clinical Hospital of University of São Paulo, São Paulo; 3Neurology Department, Fluminense Federal University and Masters Program in Science Rehabilitation, UNISUAM, Rio de Janeiro; 4Memory and Aging Unit, Geriatric Service, Department of Clinical Medicine and Cognitive Disorders Reference Center, University of São Paulo School of Medicine, São Paulo SP, Brazil

Abstract

Alexia with agraphia is defined as an acquired impairment affecting reading and writing ability. It can be associated with agraphia, but can also occur as an isolated entity. This impairment has classically been associated with a left angular gyrus lesion. In the present study, we describe a case involving a patient who developed alexia with agraphia and other cognitive deficits after a thalamic hemorrhage. In addition, we discuss potential mechanisms of this cortical dysfunction syndrome caused by subcortical injury. We examined a patient who presented with alexia with agraphia and other cognitive deficits due to a hemorrhage in the left thalamus. Neuropsychological evaluation showed attention, executive function, arithmetic and memory impairments. In addition, language tests revealed severe alexia with agraphia in the absence of agraphia. Imaging studies disclosed an old thalamic hemorrhage involving the anterior, dorsomedial and pulvinar nuclei. Tractography revealed asymmetric thalamocortical radiations in the parietal region (left > right), and single photon emission computed tomography demonstrated hyperfusion in the left thalamus that extended to the frontal and parietal cortices. Cortical cognitive deficits, including alexia with agraphia, may occur as the result of thalamic lesions. The probable mechanism is a diaschisis phenomenon involving thalamic tract disconnections.

Introduction

Alexia (or dyslexia) is defined as an acquired impairment affecting reading ability.1 Alexia is traditionally classified according to the site of anatomic damage and the presence or absence of deficits in writing (agraphia) and oral language (aphasia). In most cases, alexia and agraphia are associated with aphasia, but the dissociation is possible. Cases without aphasia are divided in alexia without agraphia (pure alexia), that has been associated with left occipital damage and alexia with agraphia, with lesions involving the left angular gyrus.2 Alexia with agraphia was first described by Déjérine in a patient with a left angular gyrus lesion. According to Déjérine, the left angular gyrus was the region where visual images of letters and words are stored, and lesions involving the left angular gyrus or the disconnection of this gyrus from other areas could cause reading and writing deficits.3 Later, Geschw ind proposed that the left angular gyrus might function as a cross-modal associative area that could convert written language into spoken language and vice versa.4,5 However, some authors have argued that the reading component of the syndrome is caused by damage to the adjacent lateral occipital gyri;6 thus, isolated left angular gyrus lesions would cause agraphia but not alexia.7

The purpose of written words is to convey sound and meaning to the reader. The reader needs to correctly see and identify the letters of a word and synthesize them into the orthographic form of the word, which creates a perceptual system. After orthographic synthesis, sound and meaning are extracted from the word, which constitute a semantic and phonological system. Disruptions in the orthographic synthesis system can cause peripheral alexia, whereas disruptions in the semantic and phonological system can cause central alexia.8 In central alexia, perceptual orthographic processing is preserved. However, downstream processing of the early visual areas that interact with more general language regions (e.g., regions that process lexical, phonological and/or semantic information) is impaired.9

The current cognitive and linguistic model of reading segregates a lexical and a sublexical route. The sublexical pathway is used to process words that follow a grapheme-phoneme correspondence (regular words for which the spelling corresponds to the sound according to grammatical rules), whereas the lexical pathway is used to optimize the processing of irregular words (words that do not follow grapheme-phoneme correspondence but rather represent an exception to standard grammatical rules [e.g., YACHT]). Currently, a parallel distributed processing approach was proposed, which states that both systems are used for all words with different degrees of semantic activation.5,10 Although the precise neural correlations that comprise the reading system are unknown, a recent functional magnetic resonance imaging study10 mapped the direct conversion of orthography to phonology to a system involving the left supramarginal, posterior middle temporal and fusiform gyri. Semantic processing has been mapped to the left middle temporal gyrus, inferior temporal sulcus, bilateral angular gyrus and precuneus/posterior cingulate. To the best of our knowledge, there is only one report of a thalamic lesions causing alexia with agraphia.11 Herein, we report a patient presenting with alexia with agraphia and other cognitive deficits caused by a hemorrhage in the left thalamus, and we discuss the pathophysiology of this syndrome.

Case Report

An 86-year-old right-handed woman with 4 years of formal education presented at our outpatient memory clinic complaining of forgetfulness, reading and writing impairment and difficulties with performing complex routine activities. Despite her low education, her former writing abilities were considered to be...
adequate when evaluated through a letter she had written 5 years before the onset of her symptoms (Figure 1). The deficits started suddenly, 17 years prior, but no diagnosis was made at that time. Immediately after the deficits began, the cognitive impairment forced her to retire from her work as a dressmaker; however, she has remained stable since then. Her prior medical history included depression, arterial hypertension and dyslipidemia. A neurological exam showed a mildly unstable gait and a right superior homonymous quadrantanopia. Bedside cognitive testing revealed alexia, agraphia and acalculia, but there were no indications of aphasia, neglect, finger agnosia or left-right disorientation. Acalulia was characterized by disabilities in arithmetic mental operations with preservation aspects of semantic and conceptual-related values (Table 1). Formal neuropsychological tests also showed deficits in attention, executive function and memory (Table 2). Language testing revealed deep alexia and agraphia in the absence of aphasia.

A magnetic resonance examination performed with a 3T magnet disclosed a T2-hypointense residual lesion in the left thalamus involving the anterior, dorsomedial (DM) and pulvinar (Pu) nuclei. In addition, there was associated volume loss, which was more evident in a susceptibility-weighted image (Figure 2A). There were no apparent cortical lesions or focal cortical atrophy.

Diffusion tensor imaging revealed an asymmetry between the left and right posterior thalamic radiations (PTRs); specifically, the left PTR was smaller than the right PTR (Figure 2B). Measurements of fractional anisotropy (FA) in regions of interest, which were primarily over both PTRs, yielded some difference (FA values on the right and left were 0.44±0.164 and 0.40±0.178, respectively). We also observed asymmetry in the postcommissural fornix (i.e., smaller on the left), which was likely due to an anterior and inferior extension of the hemorrhagic lesion. In addition, the left mammillary body was smaller than its counterpart in the right hemisphere (Figure 2C).

Single photon emission computed tomography (SPECT) showed hypoperfusion in the left thalamus and basal ganglia that extended to the frontal and parietal cortices (Figure 2D).

**Table 1. Acalculia assessment.**

| Acalculia assessment                        | 12/12 |
|---------------------------------------------|-------|
| Lexical decision                            |       |
| Numbers - written letters                   | 12/12 |
| Numbers - written in Arabic characters      |       |
| Numerals - oral verbal                      | 12/12 |
| Signs of operation                          | 12/12 |
| Total score                                 | 4/448 |
| Pairing                                     |       |
| Designation of numbers (Arabic)             | 12/12 |
| Designation of numbers - letters            | 0/12  |
| Designation of operating signals            | 0/12  |
| Total score                                 | 12/36 |
| Transcoding                                 |       |
| Dictation (letters)                         | 0/12  |
| Dictation (numbers)                         | 9/12  |
| Transcription (letters)                     | 1/12  |
| Reading (numbers)                           | 9/12  |
| Total score                                 | 19/48 |
| Count                                       |       |
| Order directly                              | 12/12 |
| Reverse order                               | 1/12  |
| Recognition sequences                       | 3/12  |
| Total score                                 | 16/58 |
| Understanding of quantities                 |       |
| Compared two by two                         | 12/12 |
| Estimated results                           | 0/12  |
| Calculation                                 |       |
| Mental calculation                          | 0/12  |
| Operations                                  | 0/12  |
| Total score                                 | 0/24  |

**Table 2. Neuropsychological test results. Standard deviation scores are given in parentheses (score[SD]), 12-15**

| Neuropsychological test | DRS | DRS - Total score |
|-------------------------|-----|-------------------|
| Attention               | 28 (-3.98) | 97 (-3.75) |
| Initiation/perseveration| 21 (-3.00) |               |
| Construction            |     | nl |
| Conceptualization       |     | nl |
| Memory                  | 11 (-4.45) |               |
| DRS - Total score       | 97 (-3.75) |               |

**Discussion**

Our patient presented with severe reading and writing impairments without aphasia. A language evaluation demonstrated a dissociation of reading-writing and oral language abilities. She had the ability to read and write only
a few high-frequency words in Portuguese (e.g., teacher, woman, dish, leg, doctor). She showed severe impairment in the reading and writing of nonwords. In the Portuguese reading task, she made some visual errors when reading moça (girl) instead of mosca (fly) or gilete (razor) by girafa (giraffe) seeming to have a tendency to guess the word based on the first phoneme. Although her skills in reading and writing were severely damaged, during a conversation she was able to construct grammatically correct sentences in length from 5 to 7 words and repeat sentences without difficulty. She showed preservation of auditory comprehension (comprehension impairment of complex material and texts may be attributed to executive difficulties).

Cognitive and behavioral consequences of a thalamic lesion may be explained by the disruption of fiber systems that link the thalamic nuclei with other brain regions or fiber systems that pass through the thalamus. In addition to this explanation, cognitive and behavioral systems may be remotely affected through diaschisis, in which lesions in one brain region produce functional impairment in a distant but interconnected brain region. Thalamocortical diaschisis is hypothesized to occur through either direct or indirect mechanisms within cortical-subcortical networks. The direct mechanism theory states that function is distributed between the cortex and subcortical structures, and lesions that interrupt the network may cause a loss of function normally carried by these networks. The indirect theory hypothesizes that a loss of activation or selective engagement (a thalamic mechanism that selects specific cortical areas to be activated to perform a given function) is responsible for thalamocortical diaschisis. Cognitive impairment may be a secondary consequence of a deactivated or disengaged cortex. The diaschisis phenomenon in thalamic hemorrhages may be temporary, with gradual improvement in the function of the affected area, but can also be persistent.

DM, lateral posterior (LP) and Pu thalamic nuclei have been called the associative thalamus because of their strong anatomic link with associative cortices and participation in high-level cognitive functions. The LP nucleus has connections with the posterior parietal cortices, medial and dorsolateral extrastriate cortices and paralimbic regions in the posterior cingulate and medial parahippocampal regions. The DM thalamus has connections with the prefrontal cortex (including the paralimbic orbitofrontal region and the associative dorsomedial and dorsolateral cortices), amygdala, basal forebrain, and olfactory and entorhinal cortices. The Pu is the main component of the posterior nuclei and can be divided into three main parts: the mediodorsal pulvinar (PuM), which projects to the parieto-occipital cortex, the prefrontal cortex, the cingulum, and the parahippocampal cortex, and the inferior pulvinar (PuI) and lateral pulvinar (PuL), which both connect to the occipital, posterior parietal and temporal lobes. The Pu is strongly associated with visual processing that is linked with areas in the temporal lobe that are involved with visual feature discrimination as well as ventrolateral and ventromedial extrastriate areas, which are involved in the analysis of visual motion. Additionally, a frequent sign of pulvinar lesions is homonymous horizontal sectoranopia due to involvement of the lateral geniculate body. Anatomical studies of the inferior parietal lobes (IPL) of rhesus monkeys have demonstrated a specific pattern of connectivity with thalamic nuclear groups. Within the IPL, area PF (as defined in references 28 and 29) has connections with the pulvinar oralis, lateral posterior and pulvinar medialis, whereas area PG has connections with the pulvinar medialis and lateral posterior pulvinar. In addition, area PG-Opt has connections with the pulvinar medialis and lateral posterior. In humans, areas PF and PG of the IPL are localized in the supramarginal and angular gyrus, respectively, where lesions have been classically associated with alexia with agraphia.

Magnetic resonance imaging of our patient revealed a left thalamic lesion involving the anterior, DM and Pu nuclei (Figure 2A). We hypothesized that the thalamic lesion affecting the Pu nucleus, may have had a secondary negative effect in cortical areas of the IFP related to reading and writing abilities. In addition, tractography indicated structural derangement of the left posterior thalamic radiations, which can be appreciated visually (Figure 2B) and through FA measurements.

In addition to hypoperfusion in the thalamus, a SPECT analysis in the present case confirmed hypoperfusion in the frontal and parietal regions, which probably indicates a functional impairment of the cortex. This impairment was likely a consequence of the thalamic lesion and structural disconnection of the cortical afferent fibers that typically join...
the thalamus and frontal and parietal cortices. Alternatively, the hypoperfusion could be secondary to the loss of activating stimuli or selective engagement from the thalamus, which would lead to decreased neuronal activation and synaptic dysfunction (i.e., a diaschisis phenomenon). 22,30 Similar to our patient, previously reported cases of pure apraxic agraphia, 31 pure agraphia, 23,32,33 and alexia with agraphia 11 due to a thalamic lesion have shown hypofunction in the ipsilateral cerebral hemisphere. Araki et al., reported two patients with alexia with agraphia due to left thalamic strokes involving the territory of the tuberoinfundibular and paramedian arteries (lesion involved the DM nucleus in both cases). In addition, both had memory and naming problems. One patient (case #1) showed hypometabolism in left frontal and parietal cortices on positron emission tomography (PET). The second patient (case #2) had a prior left medial occipital stroke but develop alexia with agraphia due to the thalamic stroke. The authors hypothesized that a secondary negative effect on cortical function in the ipsilateral temporal and parietal lobes may be the responsible for the agraphia with alexia. 11

Memory, attention and executive function deficits may also be explained by thalamic lesions and have been associated with language impairment in thalamic lesions. 34 Two intrathalamic fiber systems are distinctly related to learning and memory: 20 the ventral amygdalofugal pathway, which connects the amygdala with the DM nucleus, and the mamillothalamic tract, which connects the anterior thalamic nuclear group with the mammillary bodies. The mammillary bodies are linked with the hippocampus and entorhinal cortex. 20,23,27 In the present patient, the DM and anterior thalamic nuclei were affected by the hemorrhage, which likely contributed to her amnesia by disrupting the amygdalofugal pathway and the mamillothalamic tract. A mamillothalamic lesion, which can be identified by an asymmetry between the left and right mammillary bodies (Figure 2C), further contributed to her learning and memory impairment. Moreover, DM nucleus has strong reciprocal connections with the prefrontal cortex, explaining the attention and executive function deficits found in the patient. 25

The present study has some limitations. One limitation was that the patient only had four years of formal schooling (a fairly common finding in elderly Brazilians), which could have impaired her performance in neuropsychological and language tests and cast doubt over her previous ability to read and write fluently. Also, we don’t have a premorbid formal evaluation of her writing and reading skills. However, the patient and her family confirmed that she was able to read and write fluently (Figure 3 comparing her past and current handwriting). In addition, her performance after the hemorrhage was so severely impaired that her deficits could not be explained by her low level of schooling. Moreover, the results of the neuropsychological tests were scored according to standards set by education, according to Brazilian recommendations. 25 Another limitation was that our initial evaluation of the patient occurred 17 years after the acute deficit, and we did not have access to clinical and neuropsychological data from this extended period. Since we began evaluating the patient in 2008, her scores on cognitive and functional scales have remained stable, and she presented a non-progressive course since the beginning of the disease, what would be very unlikely in a degenerative disease. Although aphasia was not present in our current language evaluations and we have no arguments that suggested she had aphasia, we cannot affirm that the patient did not have a transitory or subtle aphasia in earlier stages of her condition, in spite of her family had denied an evident aphasia. Finally, some of the theoretical data presented in discussion are based in Japanese and English language, which have a different weighing of orthographic-to-phonologic mapping and may have distinct neural correlates than Portuguese language, which have a different weighing of orthographic-to-phonologic mapping and may have distinct neural correlates than Portuguese language.

Table 3. Language performance. Standard deviation scores are given in parentheses (score[SD]). 16-18

| Language performance | Score case | Score normal controls |
|----------------------|------------|-----------------------|
| Oral comprehension tasks |            |                       |
| Word discrimination | 14/16      | 15 (0.79)             |
| Commands             | 10/10      | 9.6 (0.50)            |
| Complex ideational material | 2/6     | 5 (0.84)              |
| Oral expression tasks |            |                       |
| Automated sequences  | 4/4        | 3.36 (0.35)           |
| Repetition of words  | 5/5        | 5 (0)                 |
| Repetition of sentences | 2/2     | 1.93 (0.25)           |
| Responsive naming    | 10/10      | 9.8 (0.41)            |
| Symbol and letter discrimination | 11/12 | 11.33 (0.42) |
| Object description*  | 6          | 7.9 (2.6)             |
| Generative naming    | 5          | 10.5 (3.1)            |
| Confrontation naming | 10         | 12.7 (2.3)            |
| Concept definition*  | 42         | 35.3 (12.8)           |

Reading tasks
- Letter/word matching | 3/4 | 4 (0)
- Picture/word matching | 1/4 | 3.80 (0.41)
- Word reading | 0/15 | 14.6 (1.55)

Writing tasks
- Shape letter | 8/14 | 13.26 (1.43)
- Correct choice of letters | 10/21 | 20.06 (1.05)
- Motor skill | 8/14 | 13.93 (0.25)
- Primer-level dictation | 1/4 | 3.93 (0.25)
- Regular words dictation | 0/2 | 2 (0.65)
- Irregular words dictation | 0/3 | 2.6 (0.63)

Note: * indicates that the test was performed with日本語, which has a different weighing of orthographic-to-phonologic mapping and may have distinct neural correlates than Portuguese language.

Figure 3. A) A note wrote by the patient 5 years before de lesion. B) The same words were dictated to the patient, showing her current impairment in writing.
Portuguese language. Although Portuguese is a language considered regular, because it provides high frequency of grapheme-phoneme conversion governed by grammatical rules, there are irregularities, for a few particular graphemes, which allow the application of the dual route model for studies of dyslexia in patients speakers and readers of Portuguese.36,37

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