Alexia without agraphia

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Introduction

This article includes discussion of alexia without agraphia or word blindness. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

Alexia without agraphia is a dramatic disorder of higher visual function in which patients can still write but are unable to read. This has been variably conceptualized as a disconnection syndrome or a word-form agnosia. In this article, the author reviews the clinical features, causes, and pathophysiologic arguments of this condition.

Key points

• Alexia without agraphia is due to a left occipitotemporal lesion.
• Alexia is often but not always accompanied by right hemianopia.
• Alexia may be either a disconnection syndrome or a selective word form visual agnosia.
• The differential diagnosis of alexia includes reading problems due to hemianopia, attentional deficits, eye movement abnormalities, and linguistic problems.

Historical note and terminology

Acquired alexia is the loss of efficient reading for comprehension, despite adequate visual acuity. Alexia without agraphia refers to a specific form, in which the ability to write is preserved, as are auditory and verbal aspects of language.

In the late 19th century, Déjérine first described this entity in a man with associated incomplete right homonymous hemianopia from a lesion of the left fusiform and lingual gyri. He subsequently deduced that the left angular gyrus stored the visual representation of words (needed for reading and writing), and that disconnecting the visual inputs of both hemispheres from the left angular gyrus could disrupt reading but leave writing intact (Déjerine 1892). These conclusions were affirmed in 1965 by Geschwind in his series of cerebral disconnection theories (Geschwind 1965).

Alexia without agraphia is also known as pure alexia or word blindness. More severe cases are sometimes referred to as global alexia, whereas milder forms constitute spelling dyslexia or letter-by-letter reading.

Clinical manifestations

Presentation and course

The key sign of pure alexia is a dramatic dissociation between the inability to read and normal writing performance. Patients can write fluently and spontaneously, but cannot read what they have written. In milder cases, reading is slow and effortful, and words are read 1 letter at a time, creating a characteristic "word length effect," in which the time to read a word increases with the number of letters it contains (Bub et al 1989; Coslett et al 1993). This is referred to as letter-by-letter reading, or spelling dyslexia. In severe cases, referred to as global alexia, patients cannot read words or letters; this defect may extend to numbers or other symbols such as musical notation or map symbols (Binder and Mohr 1992; Kawamura et al 2000). Some suggest another term for this inability to read even letters: “visuographic alexia,” meaning that patients are unable to map the visual letter symbol to its abstract meaning (Dalmas and Dansilio 2000).

In Japanese, which has 2 different writing systems, kana (phonetically based) and kanji (nonphonetic, ideographic form), alexia can impair reading of kanji but not kana (Jibiki and Yamaguchi 1993), or vice versa (Sakurai et al 2001) or both (Sakurai 2004). Dissociations in bilingual patients can also occur, with the more recently acquired language being less affected (Ohno et al 2002), perhaps in keeping with hypotheses of right hemisphere involvement in new language acquisition. In patients with long-standing blindness, alexia for Braille can be caused by occipital lesions in the absence of somatosensory deficits (Hamilton et al 2000).
Of interest, there is evidence that patients with pure alexia are still able to recognize handwriting and font, whereas this ability is impaired in patients with right fusiform lesions associated with prosopagnosia (Rentschler et al 1994; Barton et al 2010). Di Pietro and colleagues report a multilingual patient who could easily identify the language of written words despite having difficulty reading them (Di Pietro et al 2012). Hence, some aspects of text processing are spared by the left-sided lesions of pure alexia, suggesting hemispheric specialization for the type of information being extracted from written text.

Pure alexia is often part of a triad including a right visual field defect and color anomia, which also localize to the left occipital area. The right field loss is usually complete homonymous hemianopia (sometimes only a superior quadrant anopia) with or without right hemiachromatopsia (Damasio and Damasio 1983). Pure alexia can also occur without hemianopia (Greenblatt 1973; Vincent et al 1977; Uitti et al 1984; Henderson et al 1985; Iragui and Kritchevsky 1991; Erdem and Kansu 1995). Color anomia is the impaired naming of colors, even if they are seen in the normal left hemifield, and despite the intact ability to match colors (Geschwind and Fusillo 1966; Greenblatt 1973; Vincent et al 1977; Damasio and Damasio 1983; Uitti et al 1984; Henderson et al 1985; Iragui and Kritchevsky 1991; Erdem and Kansu 1995). Naming problems may extend to other visual objects as well as objects perceived through some other sensory modality, such as touch (de Renzi et al 1987).

Verbal memory deficits and visual agnosia can occur (Damasio and Damasio 1983; de Renzi et al 1987), as well as a disconnection optic ataxia in which the right hand cannot target objects in the left visual field accurately (Damasio and Damasio 1983).

Both the onset and progression of alexia depend on the underlying lesion.

**Prognosis and complications**

Little is known about the course of pure alexia. Much of the time, course is dominated by the nature of the underlying pathology. With a stable lesion, some improvement is possible. More detailed information about the natural course with stable pathology is becoming desirable, given the resurgent interest in cognitive rehabilitative strategies for alexia.

**Clinical vignette**

A 58-year-old woman presented with a generalized seizure. Imaging revealed a tumor in the left occipital lobe, which on resection proved to be glioblastoma multiforme. She had received radiation treatment and was in remission when referred, 9 months after onset, for evaluation of increasing visual complaints. She noted profound problems with reading (especially with long words), but had no other cognitive complaints. She had a dense macular-splitting hemianopia. Reading assessment was consistent with a letter-by-letter strategy, with slowed effortful reading and more time taken with longer words. Repeat imaging showed extension of tumor and edema to the anterior and medial left occipital lobe with new involvement of the splenium, compared to films from 6 months prior. She died 2 months later.

**Biological basis**

**Etiology and pathogenesis**

Pure alexia is most always caused by lesions in the left hemisphere, most commonly in the medial and inferior occipitotemporal region (Damasio and Damasio 1983; Binder and Mohr 1992). A single case report describes the syndrome due to a right occipital lesion in a right-handed person (Robinson et al 2016). Many of these may involve the splenium or callosal fibers, an anatomic point critical to the disconnection hypothesis, but often also involve the mid-fusiform gyrus, which is key to the agnosia hypothesis (Pflugshaupt et al 2009). One small neurosurgical study suggested localization to the inferior parietal region, but given the few subjects and the variable nature of tumors regarding localization, this finding may be less reliable (Shinoura et al 2010).

The majority of alexia cases are due to left posterior cerebral arterial infarction. This usually results from thromboembolic disease involving the basilar vertebral vessels, but alexia without agraphia can rarely result from left carotid artery disease if the left posterior cerebral artery originates from the carotid artery rather than the basilar artery (fetal origin of the posterior cerebral artery) (Resende Campos et al 2003). Other causes include primary and

A right hemianopia can disrupt reading, particularly when the field loss involves the central 5 degrees of vision. This hemianopic dyslexia can be effortful and slow the speed of reading, sometimes resembling letter-by-letter reading. However, not all patients with right hemianopia have impaired reading, and cases of pure alexia without hemianopia are described too, indicating that hemianopia is not the cause of pure alexia. A study comparing word-length effects in (a) normal subjects with simulated hemianopia, (b) stroke subjects with and without hemianopia, and (c) stroke subjects with and without lesions of the left anterior fusiform gyrus suggests that acquired alexia results in word-length effects beyond that accounted for by concurrent visual field loss (Sheldon et al 2012). Another study reinforced that homonymous hemianopia alone can cause some reading deficits independent of higher order visual pathology (Bao et al 2015). It has been proposed that alexia might be accounted for by visual deficits for mid- to high-range spatial frequencies typical in text. However, testing of spatial frequency contrast sensitivity has been reported as normal in at least 1 subject with alexia (Starrfelt et al 2013a).

There are at least 3 plausible pathophysiologic explanations of pure alexia: (1) visuoverbal disconnection, (2) simultanagnosia, and (3) visual agnosia.

The traditional explanation of pure alexia is a disconnection of vision from language centers (Dejerine 1892; Geschwind 1965). When there is complete right hemianopia, the only remaining vision is in the left visual field. This is processed by the right occipital cortex; the transfer of these data to language centers in the left angular gyrus is interrupted when the occipital lesion involves callosal fibers in the splenium, forceps major, or periventricular white matter surrounding the occipital horn of the lateral ventricle (Damasio and Damasio 1983). Pure alexia without hemianopia is caused by lesions of the white matter underlyng the angular gyrus. Such “subangular” lesions cause a distal disconnection of the input from both hemispheres to the angular gyrus (Greenblatt 1973; Vincent et al 1977; Henderson et al 1985). Most of these projection fibers travel ventral to the occipital horn (Vincent et al 1977; Henderson et al 2004). It may be that the status of some dorsally traveling projections to the angular gyrus determine whether the alexia is partial (spelling alexia) or severe (global alexia) (Binder and Mohr 1992).

Some of the clearest proof of the disconnection hypothesis comes from cases with atypical lesions. Pure alexia can occur with the combination of a splenial lesion and a left geniculate nuclear lesion causing right hemianopia (Silver et al 1988; Stommel et al 1991; Tamhankar et al 2004), or of a splenial lesion in the left optic radiation (Maeshima et al 2011). These cases show that disconnection is sufficient to cause pure alexia as there is no damage to striate or extra-striate cortex to generate agnosia or simultanagnosia.

Others propose that at least some cases of alexia are a type of “ventral” simultanagnosia, in which patients can only process incomplete fragments of their visual percept (Farah 1990). Although standard tests for simultanagnosia in some patients have been negative (Warrington and Shallice 1980), there have been challenges to the adequacy of these tests for the alexic deficit (Farah 1990). Related to this concept are findings in pure alexia of reduced apprehension span for digits and numbers (Starrfelt et al 2009).

Another hypothesis is that pure alexia is a specialized visual agnosia (Warrington and Shallice 1980; Vaina 1994). The alexic deficit is magnified with brief presentation of words and cursive script rather than print (Warrington and Shallice 1980). In a single patient with pure alexia, there was increased difficulty identifying words acquired at an older age compared with those acquired at a younger age (Cushman and Johnson 2011). Along with the letter-by-letter reading strategy and the word length effect, these are explained as secondary to difficulty perceiving words as whole, unitary structures. Such a visual agnosia may not be completely specific for words. A patient with pure alexia had difficulty in perceiving complex textures, a problem with local pattern analysis that may be relevant to word perception (Rentschler et al 1994). Others have shown that alexia can be associated with subtle disturbances in visual recognition of nonverbal items (Behrmann et al 1998; Starrfelt et al 2010). This agnosia may be restricted to the visual domain; when tested on imagery of letters and words, a patient was able to do much better when allowed to trace letters manually than when he was asked to manipulate visual images of letters mentally (Bartolomeo et al 2002). A visual word-form agnosia may also explain findings that some patients with apparent “pure” alexia actually do have some more subtle writing problems. This consists of a surface dysgraphia, in which their spelling relies on phoneme-t-
-grapheme rules. They have trouble with words with irregular spelling, like “yacht” and “colonel” (Rapcsak and Beeson 2004; Sakurai 2004). This suggests that they have trouble accessing an internal lexicon for writing purposes too.

Studies with functional magnetic resonance imaging suggest the existence of a visual word form area in the left fusiform gyrus (McCandliss et al 2003), which connectivity analyses show is a component of a larger network involved in reading (Reinke et al 2008). Some speculate that the agnostic form of alexia may be due to disruption or disconnection of this visual word form area (Cohen and Dehaene 2004). A contrast between patients with hemianopic dyslexia and patients with pure alexia suggested that damage to the region of the visual word form area is what characterizes the latter specifically (Pflugshaupt et al 2009). A survey of a large group of patients with left hemispheric strokes suggests that disruption of this fusiform region is specifically associated with computing grapheme sequences (ie, the small letter strings that convey meaning when assembled into words) from visual input (Hillis et al 2005).

Additional support for the role of the visual word form area in pure alexia comes from studies of patients with surgical lesions examined with functional neuroimaging. These show that in patients who become dyslexic postoperatively, the lesion destroys either the visual word form area (Gaillard et al 2006) or the adjacent white and grey matter (Cohen et al 2004), possibly causing deafferentation of the word form area. In another case, loss of fibers projecting between the visual word form area and occipital cortex has been confirmed using diffusion tensor imaging tractography, providing some anatomic support for Dejerine’s hypothesis (Epelbaum et al 2008). Finally, in epileptic subjects, intraoperative cortical stimulation of a region corresponding to the left visual word form area has been shown to cause a temporary pure alexic syndrome (Mani et al 2008).

Interestingly, detailed neuroimaging studies of subjects with developmental dyslexia suggest loss of grey matter in these same fusiform regions bilaterally (Kronbichler et al 2008). In Japanese patients, alexia for kana (syllabograms) that spares reading for kanji is associated with similar fusiform lesions (Sakurai et al 2008) as well as reduced activation on fMRI (Richlan et al 2010).

Some authors propose that the inefficient letter-by-letter reading strategy of these patients reflects a substituted processing by the right fusiform gyrus (Cohen et al 2004). Others have also attributed some of the residual covert (or unconscious) reading abilities of these patients to residual right hemispheric processing (Larsen et al 2004). Functional neuroimaging has provided some support for this, showing in one patient that the right fusiform gyrus was more active during a phase of letter-by-letter reading but that with resolution and improvement of reading there was increased activity in cortex around the lesion in the left fusiform gyrus (Ino et al 2008).

**Differential diagnosis**

Pure **alexia** is the loss of reading competency. This loss distinguishes it from the more well-known entity of **dyslexia**, which is an impairment in reading competency acquisition dating back to childhood, when most people learn to read. The origins of childhood dyslexia are not related to pure alexia and remain a topic of controversy, particularly with regards to possible dysfunction of a rapid magnocellular stream of stimulus processing (Ramus 2004; Skottun 2005).

Impaired reading is a component of many aphasic disorders. Testing auditory and oral linguistic skills will readily reveal these nonvisual elements and lead to the correct diagnosis. Alexia with **agraphia** is caused by lesions of the left angular gyrus (Dejerine 1891; Benson 1985) or (sometimes) the adjacent temporoparietal junction (Kawahata and Nagata 1988). It may be accompanied by **Gerstmann syndrome**.

Similarly, reading will be impaired nonspecifically in a number of visual disorders. Patients with bilateral reduction in acuity of ocular or cerebral origin will read poorly. To avoid confusion, their acuity should be tested with a nonletter optotype, preferably gratings.

Visual field defects that do not affect central acuity can also impair reading. Bitemporal hemianopia can cause hemifield slide. The fact that no region of the visual field is represented in both eyes leads to unstable binocular alignment. As the eyes wander between esotropia and exotropia, words transiently double or disappear during reading (Kirkham 1972). Homonymous field defects affecting the central 5 degrees cause hemianopic dyslexia (Trauzettel-Klosinski and Brendler 1998). Reading left-to-right is slowed more by right than left hemianopia (de Luca et al 1996; Trauzettel-Klosinski and Brendler 1998). Patients with left hemianopia have trouble finding the beginning of lines because the left margin disappears into their blind defect as they scan rightwards (Zihl 1995; Trauzettel-Klosinski and Brendler 1998). Right hemianopia prolongs reading times, with more fixations and smaller saccades (Zihl 1995; de
Luca et al 1996; Trauzettel-Klosinski and Brendler 1998). However, the reduction in reading speed is not as severe as that due to the word-length effect in pure alexia (Pflugshaupt et al 2009). Right hemianopic alexia can be improved with an optokinetic therapy aimed at encouraging rightward saccades (Spitzyna et al 2007).

Patients with left hemineglect make left-sided reading errors known as neglect dyslexia (Behrmann et al 1990). They omit the left side of lines and make left-sided omissions, additions, or substitutions with words. Vertical text is not affected (Behrmann et al 1990). Rarely, it may occur without other signs of hemineglect (Patterson and Wilson 1990).

Abnormal eye movements may impair reading. Acquired ocular motor apraxia from bilateral frontal or parietal lesions can impair reading severely (Holmes 1918; Pierrot-Deselligny et al 1986; Husain and Stein 1988; Baylis et al 1994). Inaccurate or delayed saccades to nonverbal targets are found. Accompanying signs of simultanagnosia or optic ataxia may be present. Interruption of fixation by saccadic intrusions such as square wave jerks, ocular flutter, or opsoclonus will disrupt reading, but with careful ocular motor examination, should be obvious.

Lastly, central dyslexias are reading impairments with a linguistic basis. Patients with surface dyslexia have lost an internal dictionary and cannot pronounce irregular words like “yacht” and “colonel” (Shallice et al 1983; Cummings et al 1986). Patients with phonological dyslexia have lost generic pronunciation rules and cannot guess the pronunciation of pseudo-words or words that are new to them (Funnell 1983; Friedman and Kohn 1990).

**Diagnostic workup**

A diagnosis of pure alexia requires exclusion of significant visual or linguistic dysfunction. Visual acuity needs to be adequate, and its measurement sometimes requires gratings or other nonverbal optotypes when a severe global alexia is suspected. Standard tests of auditory comprehension and oral language output must establish the lack of aphasia. The patient is asked to write a short paragraph to exclude agraphia.

Establishing alexia is easy if the defect is severe. Reading a short passage aloud is attempted. If the patient is not able to do this, reading of simple letters or numbers is tried next. With spelling dyslexia, reading will be laborious; the examiner should listen to see if longer words take more time to read: the characteristic “word-length” effect.

Formal neuropsychological assessment is invaluable in assessing partial or subtle reading dysfunction, particularly when the examiner is unclear about interpreting the patient’s current reading ability in terms of their premorbid linguistic competency.

Neuroimaging is important to detect not only the site of the lesion, but also for clues to pathology and to direct subsequent investigations to the cause of the lesion. FDG positron emission tomography has been reported to show hypometabolism in the affected area in an individual with alexia and no lesion on MRI scan (Graff-Radoford et al 2014).

**Management**

Interest in rehabilitation of reading in alexic patients is high, with many imaginative strategies currently evolving, as reviewed by Starrfelt and colleagues (Starrfelt et al 2013b). These include altering text to highlight the spacing between words or phrases (Beeson and Insalaco 1998; Maher et al 1998), enhancing oral articulation during reading (Conway et al 1998), repetitive oral reading of text (Beeson and Insalaco 1998), attempts to enhance implicit or covert processing of whole words (Maher et al 1998; Friedman and Lott 2000; Ablinger and Domahs 2009), and finger tracing of letters (kinesthetic treatment) in patients presumed to have a disconnection syndrome (Maher et al 1998; Nitzberg and Friedman 1999). Moore and colleagues attempted therapy using a “face font” that used faces to represent phonemes and found that an alexic patient was able to learn this non-alphabetic reading system, though not at the level of control subjects (Moore et al 2014). Woodhead and colleagues were able to demonstrate functional improvements in whole word recognition that were associated with changes in reading network connectivity as measured with magnetoencephalography following therapy designed to enhance processing of whole words (Woodhead et al 2013). Lacey and colleagues reported enhancement of behavioral training following transcranial direct current stimulation therapy (Lacey et al 2015). The success of these approaches in improving both speed and accuracy requires further evaluation and will likely require tailoring to the specific reading defect in a given patient (Leff and Behrmann 2008). For example, Kim and colleagues reported poor results of kinesthetic treatment in a patient found to have both visual-verbal and kinesthetic-verbal disconnections (Kim et al 2011).
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**References especially recommended by the author or editor for general reading.

**Former authors**

Jason J S Barton MD PhD (original author)

**ICD and OMIM codes**

**ICD codes**

ICD-9:
Alexia (congenital) (developmental): 315.01
Alexia, secondary to organic lesion: 784.61

ICD-10:
Dyslexia and alexia: R48.0

**Profile**

**Age range of presentation**

0-01 month
01-23 months
Sex preponderance

male=female

Family history

none

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

dyslexia
alexia with agraphia
Gerstmann syndrome
bilateral reduction in acuity of ocular or cerebral origin
bitemporal hemianopia
hemianopic dyslexia
neglect dyslexia
left hemineglect
abnormal eye movements
acquired ocular motor apraxia
optic ataxia
square wave jerks
ocular flutter
opsoclonus
central dyslexias
surface dyslexia
phonological dyslexia

Associated disorders

Global alexia
Pure alexia
Spelling dyslexia

Other topics to consider

Acalculia
Alexia
Extrasylvian aphasias
Perisylvian aphasias
Visual agnosias

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