The significance of aphasia in neurological cancers

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Aphasia associated with brain tumours has previously been regarded as essentially equivalent to the aphasia of stroke, and as a deficit unlikely to affect a patient’s prognosis. Recent research challenges such hypotheses. Tumour-related aphasias are commonly amnestic aphasias, and hence pathologically distinct from classic post-stroke aphasias. Accordingly, many rules from the world of stroke cannot be readily translated to the management of tumour-related aphasia. Furthermore, aphasia may be an important clinical prognostic parameter in neuro-oncology. Tumour-related aphasia is associated with an increased risk for developing depression, poorer coping and reduced survival time. It is important that health professionals are aware of the unique pathology and prognostic significance of neuro-oncological aphasia, and of strategies available for its relief.

Introduction

A diagnosis of a brain tumour (whether primary or secondary) is devastating, due not only to the life-limiting nature of the diagnosis, but also the impact of attendant symptoms. Brain tumours may cause distressing symptoms such as intractable vomiting, new-onset seizures, severe headaches, hemiplegia or aphasia. [1] In the maelstrom of scheduling surgery and radiotherapy or organising complex chemotherapy regimens, the significance of an aphasia may be overlooked.

In the presence of neurological disease, multiple patterns of aphasia may develop due to the complex neuroanatomy of language in the human brain. Tumour-related aphasia is a distinct pathologic entity. Its typically amnestic nature reflects the generalised hypometabolism induced by a brain tumour, and differentiates it from the more site-specific aphasias of acute events such as stroke.

In terms of prognosis, aphasia worsens patients’ quality of life and may shorten survival time. [2] Understanding and tackling tumour-related aphasia is therefore very important. Active treatment with speech pathology and medications, as well as minimising iatrogenic aphasia, best optimises language outcomes for patients diagnosed with a neurological malignancy.

1. What is language, and where is it in the brain?

The nature of language, and its neuroanatomical equivalents, has been defined in a number of ways. In one of the most accessible scientific definitions, Szofia Bullain [3] defines ‘language’ as “the formulation, transmission, and comprehension of thoughts by verbal and nonverbal symbols.” More poetically, William Chomsky [4] delineated the power of language through his argument that, “We do not first have thoughts, ideas, feelings, and then put them into a verbal framework. We think in words, by means of words. Language and experience are inextricably interwoven, and the awareness of one awakens the other. [Language is]... as indispensable to our thoughts and experiences as are colours and tints to a painting.” Elucidating the inner workings of this neurological work of art has long been a major research goal.

Decades of cortical localisation studies reveal that the ‘language sites’ of the brain are widespread. In the classic ‘textbook’ brain, key language centres are located in the left hemisphere, adjacent to the Sylvian fissure and supplied by the middle cerebral artery and its branches. These language centres can be divided into two major functional groups – receptive and expressive. The receptive language centres (Brodmann’s Areas 22, 39, 41 and 42 [the primary auditory centre]) are a central-command neuronal network containing information about sounds, words and the meanings of relationships. These areas, exemplified by Wernicke’s Area, help understand and analyse spoken and written language. By contrast the expressive centres (Brodmann’s Areas 6, 44, and 45), typified by Broca’s Area, control the movements of the tongue, lips, and vocal cords to facilitate speech implementation. [5]

However, a simplistic ‘Broca’s and Wernicke’s’ view of the brain does not explain the full complexity of neural language processing. Almost every cortical region, as well as the cerebellum, plays a role. Regions in the temporal, parietal and occipital lobes all aid the sequencing of auditory records of oral language and visual representations of written language into neural word representations. [6] The supplementary motor cortex helps initiate and plan speech output, [7] while the right hemisphere contributes an understanding of prosody (the significance of variations in tone and pitch), and the cerebellum integrates the motor components of speech output. [8]

The neural geography of language is thus not nearly as reductionist as two localised zones in the left hemisphere. Rather, neurologist Aleksandr Luria [9] proposed that language is best understood as a functional system that, when mapped anatomically, forms an intricate ‘cortical constellation’ of dispersed loci.

Variation in the language constellation is fairly common, and may be either idiopathic or induced by neuropathology. In 1978, Ojemann [10] demonstrated that the topography of language cortex in any individual healthy person is often markedly different to the aforementioned ‘textbook’ maps. Pathology is also a powerful driver for variation in language localisation. Early seizure onset may displace language functions out of the temporal lobe and into the parietal lobe or right hemisphere. [11] Remarkably, in people with congenital focal lesions in the left hemisphere, the developing brain may even react by forming a mirror-image organisation of the entire cerebro-cerebellar linguistic network. In such people, language production is represented entirely homotopically to the normal left-hemisphere-dominant arrangement. [12]

Neurological malignancies are a highly pertinent example of a pathology that may induce relocation of language functions. One study of patients with gliomas and tumour-related aphasia identified that the major determinant of whether the right hemisphere successfully integrated into the language network was the rate of tumour growth
only patients with slowly-progressing gliomas were able to re-locate their language function. [13,14] In a study evaluating contralateral language in brain tumour patients, 60% of the patients exhibited activation of the right inferior frontal gyrus, while in 18% a new right hemisphere dominance was observed. [15]

2. What are aphasias and what type occurs in neurological malignancies?

As illustrated above, language is a complex entity, and lesions in different areas of the brain produce a variety of speech and language disorders. Four of the best-characterised aphasias are Broca’s aphasia, Wernicke’s aphasia, anomic aphasia and global aphasia. The hallmark of a Broca’s aphasia (due to damage at the site of Broca’s Area), is impaired speech; it is non-fluent, agrammatical and effortful, despite intact understanding. Often, the patient is aware of their errors and consequently extremely frustrated; this may be expressed through crying, screaming or yelling. In Wernicke’s aphasia (due to damage at the site of Wernicke’s Area), the patient exhibits fluent and well-articulated, but ultimately meaningless, speech. The creation of neologisms is one of the characteristic features of this class of aphasia.

Anomic aphasia (due to damage to the left temporal lobe, but also caused by multiple other lesions) is often mistaken for a Wernicke’s aphasia, since again the patient has intact repetition and fluent speech. However, the key problem here is a difficulty in finding words and naming objects. In global aphasia (due to damage involving both Broca’s and Wernicke’s Areas and most of the region between them), the deficit affects all aspects of language. The patient usually understands only a few words or phrases, and may be able to say a few words or imitate a few sounds. Usually, they are absolutely unable to read or write. Emotionally, the patient is frequently depressed.

If the pathways connecting the major language centres are destroyed, a ‘disconnection syndrome’ is seen. The two best-described ‘disconnection syndrome aphasias’ are conduction aphasia and transcortical aphasia. In conduction aphasia (due to the disconnection of the receptive and expressive areas), the patient has relatively fluent speech, word-finding difficulties, variable reading and writing abilities and poor repetition. In transcortical aphasia (due to the disconnection of the peri-Sylvian language areas from the cerebral cortex), the patient has intact repetition but experiences problems in producing spontaneous speech or understanding spoken language. [3]

Most of the scientific literature on aphasia is based on studies performed on stroke survivors. Classically, these patients were believed to develop a stereotyped ‘vascular aphasia’ (Broca’s, Wernicke’s, transcortical or Wernicke’s aphasia) secondary to infarct of the vascular territories of the superior or inferior division of the left middle cerebral artery respectively. [16] However, new technologies – such as positron emission tomography (PET) scanning, functional magnetic resonance imaging (fMRI) and magnetoencephalography – have revealed that the classical lesion symptom correlations are in fact significantly less predictive than expected [17], with localised aphasias potentially associating with widespread damage and vice versa. With sophisticated modern imaging, post-stroke aphasias may now be meticulously delineated, and the geographical complexity of aphasia appreciated.

There is a lesser volume of research into tumour-related aphasia, but current findings suggest that tumour-related aphasia differs fundamentally from those of stroke. Many of the new lessons learnt from post-stroke aphasia cannot be generalised to the management of neoplastic aphasia, and there is a real need to expand the volume of aphasia research focusing specifically on brain tumour patients.

Aphasia is common in the world of brain tumours. Dominant hemispheric primary brain tumours cause aphasia in 53% of patients. [18] Tumour-related aphasia is typically mild, with anomic aphasia the most common subtype – and this prevalence of an anomic aphasia occurs regardless of the tumour’s exact location or grade. [19] The reasons for the dominance of anomic aphasia, and independence of tumour location and aphasia type, are thought to be tied to the histopathological nature of brain tumours.

The pathology of tumour-related aphasia is markedly different to post-stroke aphasia. One of the major causes of this difference is the temporal profile of a brain tumour (chronic) compared to a stroke (acute). It is hypothesised that the gradual progression of brain tumours allows for linguistic reorganisation during tumour growth, but this reorganisation cannot occur in the setting of an acute neurologic insult, such as a stroke. [20] This mechanism fits well with the discovery that the rate of tumour growth is the key variable influencing language relocation. In the clinical setting, an excellent example of this hypothesis is seen with lesions of the fronto-parietal operculum. Typically, a stroke in this area produces a Broca’s aphasia whereas a tumour at the same site will not, presumably since the brain has had enough time to relocate the necessary language functions. [21]

The second reason why there is such dissimilarity between vascular versus neoplastic aphasia is that, in each situation, the mechanism of neuronal injury is completely different. Characteristically, a stroke is a devastating injury that drives the brain tissue to infarct. By contrast, brain cancers grow by infiltration and displacement, only damaging neurons in the later stages. Recent research using PET scanning to investigate the nature of neuronal injury at this stage has elucidated that brain cancers appear to induce a generalised hypometabolic state in both the peri-tumoural area as well as regions that are distant from the cancer. [22] This explains both the relative mildness of tumour-related aphasia and the unimportance of exact tumour location; rather than creating a discrete zone of infarcted tissue, brain tumours induce a generalised depression of neuronal function.

3. Does aphasia really affect a patient (who is already dealing) with brain cancer?

As Ludwig Wittgenstein insightfully declared, [23] “The limits of my language stand for the limits of my world.” The ability for expression with spoken words and writing makes humans unique. Language and speech not only facilitate our interpersonal interactions but also, as Chomsky stressed, are an integral part of cognition. When these critical brain functions are disrupted or lost, the result is devastating. There could hardly be a worse time in life to lose the capacity for language than when one is battling a brain tumour. Dealing with cancer requires language facilities of a highly sophisticated level, as patients navigate a complicated healthcare system, provide informed consent to complex procedures, identify problems with treatment and learn new self-care measures.

For those patients who survive their brain tumour, it is well-documented that deficits in language impair the ability to return to work, or even perform routine daily activities. For those patients whose tumour is incurable, a language deficit is a source of great frustration when trying to communicate meaningfully with much-loved family and friends in final weeks. [24] To return to the poignant words of Wittgenstein, to experience one’s language vanishing is to be forcefully reminded of how the limits of one’s world are inexorably shrinking.

Aphasia perse is an extremely distressing problem, and a real trigger for depression. People with aphasia experience a lower health-related quality of life, with reduced activity levels, level of independence, social relationships and access to aspects of their environment. [25-7] One study found that 50% of patients with aphasia showed significant depression, as measured by four different depression scales. The prevalence of depression correlated well with degree of insight remaining. [28]

It is perhaps unfortunate, therefore, that patients with tumour-related aphasia usually do retain their insight and intellectual ability. Haas’ study [29] into the intellectual abilities of patients with neoplastic aphasia found that “the intellectual performance in aphasic patients
with brain tumours was impressive... We found no differences in the intellectual performances between aphasics, non-aphasics with left-sided tumours and patients with right-sided tumours.” While in the larger picture it is usually beneficial to retain intellectual capacity, sadly in the context of aphasia it means these high-performing patients with tumour-related aphasia are especially vulnerable to severe depression. Neoplastic aphasia may thus lead to adverse psychological outcomes over and above those that would already be anticipated in a person diagnosed with a brain tumour.

However, the true malignant potential of tumour-related aphasia is not confined to creating poor quality of life and a high risk for depression – aphasia may even worsen the prognosis of patients with neurological malignancies. One study of 116 patients with high-grade glioma [2] analysed speech deficit as a subdivision of global functional status in terms of incidence, category and prognosis for survival. Patients with speech deficit had significantly poorer median survival (six months) compared to those with intact speech (10.5 months). These findings are supported by Meyers, [30] who showed that a multifaceted set of ‘quality-of-life’ parameters, including language deficits, effectively predicted for survival. Meyers suggests that these newer prognostic variables should now be included alongside more standard clinical indices, such as tumour grade.

4. What can doctors and medical students do?

The nature of tumour-related aphasia is unique and important, and traditional models of understanding borrowed from stroke medicine need to be replaced with brain-tumour-specific paradigms. However, the role of the clinician or medical student can successfully extend far beyond merely appreciating the unusual nature of tumour-related aphasia. Doctors can improve their management of neoplastic aphasia in two major ways: by actively promoting return of language function, and by anticipating and avoiding iatrogenic damage.

a) Therapies for aphasia

Oncology teams can now target aphasia with intensive speech pathology and even medication. With 30-50% of brain tumour patients suffering aphasia, the speech pathologist is an essential member of the neuro-oncology unit. At diagnosis, the patient’s degree of deficit should be assessed and scored, coping strategies devised and communication therapy instituted for best outcome. [2] Recent studies have found that intense treatment over a short period is more efficacious than low-intensity therapy over a longer time-course. [16]

Another new possibility in aphasia therapy lies in emerging medical treatments. Studies show that taking bifemelane (a cholinergic agent) 300mg daily can improve fluent aphasia (such as Wernicke’s and anomic aphasia), while bromocriptine (a dopamine agonist) creates significant improvement in non-fluent aphasias (such as Broca’a aphasia). [3] Transcranial magnetic stimulation has also been proposed to offer benefits, with encouraging findings from several recent small case series. [31,32]

References

Medical cancer therapies such as chemotherapy and radiotherapy are also implicated in worsening aphasia. [34] In children treated with cisplatin or carboplatin for brain tumours, an increased incidence of hearing loss is linked to poor language development. Sodium thiosulfate, known to reduce the incidence of platinum ototoxicity in adults, is currently being investigated for its applicability to a paediatric population. [35,36] Radiotherapy can also impair language ability, again particularly when the patient is young. [37] One study showed that when radiation dose was doubled from 18 Gray to 36 Gray, the patient’s intelligence quotient (IQ) decreased by a mean value of twelve points. Consequently, many oncology teams now refuse radiotherapy to children under three years old, and limit radiation to the minimum effective dose for others. [38]

Conclusion

Aphasia is common in the world of neuro-oncology, occurring in 53% of patients with dominant-hemisphere tumours, and it is critical that health professionals are confident in their approach to it. Recent findings have identified tumour-related aphasia as a unique pathologic phenomenon, and also a major quality-of-life issue with real prognostic significance. It is essential that aphasia not be considered an incidental neurological deficit only of esoteric interest. Many interventions are available, and oncology teams should be aware of their powers in helping to relieve and minimise aphasia in brain tumours.

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Conflicts of Interest

None declared.

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