

Verbal Fluency Test In Patients With A New Brain Tumour

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Research Article

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Abstract

Aims: To evaluate the frequency of impairment on semantic verbal fluency (SVF) test in patients with a new brain tumour prior to neurosurgery and to examine scores across symptom presentations.

Methods: This is a secondary analysis of clinical, cognitive and capacity data from a prospective study of consent in patients with newly diagnosed brain tumours. Addenbrooke's Cognitive Examination-Revised version, which includes within it the Mini-Mental State Examination (MMSE), was tested prior to surgery. Patient's presenting symptoms were categorised into five groups according to a pre-defined criteria. SVF score was converted to a z-score to identify frequency of impairment and raw scores for SVF were compared across symptom presentations. **Results:** A total of 97 patients (51% female; mean age 53.8 years; 53% high-grade tumours; 11% metastases) were assessed. Forty-one percent had headache only or headache "plus", 26% had focal deficit only; 21% had seizures only, and 13% had cognitive deficits. SVF was impaired in 40% of patients. Adjusted SVF performance was worse for patients with headache symptoms and cognitive deficits than those with focal neurology only or seizures. SVF and MMSE had a positive moderate-strong correlation ($r=0.59$, $p<0.0001$). **Conclusion:** Decreased cognitive performance as identified by SVF is common in patients with a new brain tumour, especially those with headache or cognitive deficits. A low SVF may be a useful rapid additional "red flag" for patients with a suspicious headache, when referral to secondary care is considered. Further work needs to be done around the cut-off values for SVF in helping primary care clinicians select patients for early referral.

Introduction

Suspecting a brain tumour can be a challenge in primary care. A third of patients with a brain tumour consult their primary care clinician on three or more occasions before hospital referral [1]. Brain tumour patients have the highest frequency of emergency department presentations of all cancers. According to National Cancer Intelligence Network [2], 61% of patients with a new brain tumour were diagnosed as an emergency in England between 2006 and 2013, while only 1% were referred by primary care to secondary care via 2-week wait referral pathway while 17% are referred by a standard referral which could take significantly longer.

Initial symptoms due to a brain tumour can be focal neurological e.g. seizure, unilateral weakness, sensory loss, or more common and less alarming e.g. headache, subtle cognitive or personality changes [3]. Headache as the first symptom is reported in up to a quarter of brain tumour patients [4], yet the absolute risk of a brain tumour being the cause of a headache presentation in primary care is only 1 in 1,000 [5]. Subtle cognitive or behavioural changes can be a primary symptom for some tumours, but are rarely complained of by the patient [6] but are often noted by caregivers [7] and identified in hospital through formal assessments [4]. Patients with such subtle cognitive and behavioural symptoms will be most diagnostically challenging in primary care, and a significant proportion will ultimately present to emergency services after focal neurological signs develop. A recent report of 205 brain tumour patients diagnosed via the emergency department showed 40% of presenting symptoms were due to headache or cognitive changes [8]. In another study of patients with the most aggressive primary brain tumour

(glioblastoma multiforme) [9], the main presenting complaints were cognitive in over a quarter of patients presenting to the emergency department.

Presenting complaints that are common and non-specific (cognitive, behavioural), may be multifactorial and put down to stress, rather than a “focal” intracranial cause and often leads to diagnostic delays [4, 7]. Where there is uncertainty if symptoms might be due to a brain tumour, any factors that are seen more commonly in tumour patients (“red flags”) could be useful. A simple cognitive test, semantic verbal fluency (SVF), “how many animals can you name in a minute” score of ≤ 10 , is strongly predictive of lack of capacity to give consent to brain surgery, when compared with by a formal capacity test, MacArthur Competence Assessment Tool for Treatment, in pre-surgical brain tumour patients [10]. Semantic verbal fluency is widely used in neuro-cognitive test batteries in North American and European brain tumour trials [11]. It is thought to test executive function parameters of selective attention and mental shifting [12, 13]. Although no literature exists on cut-off values to identify mild cognitive impairment for neuro-oncological patients, studies in dementia indicate that a SVF score of 17 animals may be a concern and below 15 may suggest a mild cognitive impairment with 88% sensitivity and 96% specificity [14-16].

In primary care setting, cognitive testing is constrained by limited time of consultation. We examined the performance of this one-minute “animal” test in a cohort of brain tumour patients prior to undergoing surgery, to establish which presentations were most likely to be associated with a poor result.

Methods

This is a secondary analysis of an original prospective cohort study examining a patient’s capacity to consent for surgery. Details of this are published [10] but to summarise, patients aged at least 18 years old with a radiologically suspected brain tumour were assessed prior to neurosurgery. The study was carried out at the regional neurosciences centre for the South East Scotland at the Western General Hospital. Local research ethics committee (LREC) approval for the study was sought but deemed unnecessary by the LREC committee since the study was to assess capacity to consent to surgery, therefore no consent was necessary to enrol patients. This was therefore an unselected series of consecutive brain tumour patients, without exclusions.

For the purposes of this analysis, we identified the symptoms at hospital presentation for 97 patients involved in that study. Subjective complaints were coded according to predefined criteria: a) seizure only; b) headache only; c) headache - plus; d) neurology only; e) cognitive with / without neurological deficit. “Headache – plus” refers to headache with an additional symptom, either neurological or cognitive. “Neurological” refers to focal weakness, numbness, diplopia or hemianopia. “Cognitive” refers to memory deficit with/without dysphasia. Patients were asked to complete the Addenbrookes Cognitive Examination-Revised (ACE-R) test, which includes the Mini-Mental State Exam (MMSE) and the semantic verbal fluency (SVF). ACE-R is a brief cognitive battery designed for dementia screening and includes assessment of attention and orientation, memory, verbal fluency, language and visual-spatial skills [17].

The SVF requires that the examiner, following a short introductory explanation, asks the patient to “think of as many animals as they can within one minute, starting now”. In the ACE-R scoring system, the numbers of animals are graded into seven groups, depending on the scores, however, for the purposes of this analysis we recorded the actual numbers, or raw scores. Since we did not have a comparator group we calculated age and education adjusted z-scores from published standardised age and education norms [18], in a similar approach taken by Talacchi and colleagues [19]. We elected to look at the mean and median SVF for each of the five symptom categories a) – e), the adjusted z-scores and also the frequency of test impairment in each symptom category.

Symptoms of depression and anxiety were screened for using the Hospital Anxiety and Depression Scale (HADS) [20]. We analysed the HADS scores in two groupings (normal = 0–7; Abnormal ≥ 8).

Statistical analysis

Two-sample t-tests were used to examine if there was any evidence of a significant difference in raw SVF score between age, education and gender groups separately.

One-way ANOVA looked at the relationship between symptom presentation groups and SVF z-score, and where appropriate Tukey post-hoc analysis was used to compare symptom presentation groups separately.

Patient SVF scores were converted to an individual z-score, adjusted to published age and education normative data [18], using the formula (below) to determine the frequency of test impairment. It is widely accepted in the neuropsychological research that a score ≤ -1.5 standard deviations (SD) below the mean of healthy controls is defined as a clinically significant cognitive impairment.

$$Z - score = \frac{\text{participant mean SVF score} - \text{Aged and Education matched nonrmative mean SVF score}}{SD (\text{age and education matched healthy controls})}$$

Two-sample t-tests (one-way ANOVA where appropriate) were used to examine the relationship between steroid use, AED, lesion laterality, tumour lobe and HADS with raw SVF score. If there is evidence of a statistically significant relationship, and if appropriate, Tukey post-hoc analysis was performed comparing groups within each variable separately.

The correlation between raw SVF and MMSE scores was analysed using a Pearson’s correlation. A weighted Kappa was used to measure the level of agreement between MMSE and SVF impairment groups.

The level of significance was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 21. Note that percentages may not total 100 due to rounding.

Results

Ninety-seven patients were included in the analysis. From the pre-determined categories, 21% of patients presented with a seizure only, 41% of patients had headache with or without additional symptoms, 26% of patients with focal neurology and 13% of patients with cognitive deficits (**see** Table 1).

Table 1
Patient characteristics at baseline

	n (%)
	Total = 97
DEMOGRAPHICS	
Mean age at diagnosis in years (SD)	53.8 (15.1)
16–59 years	52 (54)
60–79 years	45 (46)
Female	49 (51)
Education (N = 96)	
9–12 years	76 (79)
13–21 years	20 (21)
SYMPTOMS	
Seizure only	20 (21)
Headache only	18 (19)
Headache Plus	21 (22)
Neurology only	25 (26)
Cognitive with/without neurology	13 (13)
AED USE	21 (22)
STEROID USE (n = 94)	62 (66)
TUMOUR	
Grade	
WHO I-II	35 (36)
WHO III-IV	51 (53)
Metastasis	11 (11)
Location (n = 96)	
Frontal lobe	38 (40)
Temporal lobe	11 (11)
Parietal lobe	17 (18)
Occipital	9 (9)
Other	15(16)
Cerebellum	6 (6)
Laterality (n = 96)	
Right	45 (47)
Left	39 (41)

	n (%)
	Total = 97
Bilateral	5 (5)
Other	7 (7)
HADS-D (n = 71) Normal	63 (89)
Abnormal	8 (11)

Fifty-three percent of patients had imaging suggestive of high grade tumour (WHO III-IV), 36% had low grade and 11% had metastases. Sixty-four percent of patients were taking steroids, while 22% were taking anti-epileptic drugs for seizures.

A greater proportion of younger patients (< 60 years) presented with seizure (29% vs. 11%) while cognitive symptoms were reported more frequently in older patients (< 60 years = 8%; ≥60 years = 20%). The proportion of patients presenting with headache only or headache-plus was similar across both age groups (younger = 19% vs. older = 18%; and younger = 23% vs. older = 20%, respectively).

There is evidence that the verbal fluency scores in younger patients are significantly higher compared to those in older patients (mean diff = 4.0, 95% CI (1.3, 6.6), $p = 0.003$). We found no evidence of a difference in SVF scores across the different levels of education ($p = 0.455$), nor gender ($p = 0.302$).

On converting SVF scores to identify impairment, 75 (77%) patients' results were below average SVF test performance (as defined by a z-score being < 0), while 39 patients (40%) showed impairment (z-score ≤ -1.5).

Table 2 summarises z-scores across the different symptom presentations. A lower patient's z-score value indicates a detrimental SVF performance relative to the normative published data [18].

Table 2
Mean and standard deviation of SVF and Z scores across symptoms

Symptoms (%) n = 97	n	Impaired SVF	Mean SVF score (SD)	Mean Z score (SD)
Seizure only	20	5 (25)	17.2 (5.9)	-0.5 (1.4)
Headache only	18	7 (39)	13.3 (7.5)	-1.2 (1.5)
Headache-plus	21	10 (48)	12.9 (6.9)	-1.4 (1.5)
Cognitive with/without neurology	13	9 (69)	8.2 (4.7)	-2.3 (1.1)
Neurology only	25	8 (32)	15.6 (5.9)	-0.6 (1.4)

The mean z-scores for patients presenting with seizure and neurological deficit only were above the total mean z-score (total mean = -1.08), whereas for all other patient groups (containing headache within the symptom complex or cognitive deficit) the total mean z-score fell below (z-score= -1.2, -1.4 and - 2.3, respectively). Overall, there is evidence that z-scores were significantly different across symptom groups ($p = 0.004$). A Tukey post-hoc analysis provided evidence of significant group differences in those with complaints of cognitive problems versus those with seizure (mean difference = 1.8, 95% CI (0.4, 3.2), $p = 0.006$) or focal deficit only (mean difference = 1.7, 95% CI (0.3, 3.0), $p = 0.007$).

On examining the SVF z-scores in each of the symptom presentation groups, 69% of patients presenting with cognitive deficits were impaired, 32% with focal deficit were impaired, 48% with headache-plus were impaired and 39% with headache only were impaired (Table 2). As expected, patients presenting with seizure only were the least likely to result in a score which would deem them as impaired.

For explorative analysis, unadjusted raw SVF scores across patient characteristics are presented in Table 3. There is evidence of significant group differences in SVF performance for steroid use and absence of anti-epileptic drug use (Table 3). There is also evidence of significant differences in SVF scores across tumour grades, however, after performing a Tukey post-hoc analysis the results show a weak relationship between low and high tumour grades (mean diff = 3.5, 95% CI (0.003, 6.9, $p = 0.05$).

Table 3
Analysis of SVF score across patient characteristics

		n	Mean (SD)	Mean diff (95% CI)	p-value
Tumour grade	High	51	12.7 (6.2)	-	0.039*
	Low	35	16.2 (6.7)		
	Metastatic	11	12.0 (8.1)		
Steroid use (n = 94)	Yes	62	12.8 (6.8)	-3.3 (-6.2, -0.4)	0.024
	No	32	16.2 (6.4)		
AED use	Yes	21	19.0 (4.2)	6.4 (3.4, 9.5)	< 0.0001
	No	76	12.5 (6.7)		
Laterality (n = 96)	Right	45	14.5 (6.7)	-	0.486*
	Left	39	13.3 (6.5)		
	Bilateral	5	10.0 (6.1)		
	Other	7	15.0 (8.4)		
Location (n = 96)	Frontal	38	13.3 (6.3)	-	0.771*
	Temporal	11	12.5 (5.2)		
	Parietal	17	15.9 (6.0)		
	Occipital	9	14.8 (9.9)		
	Cerebellum	6	13.8 (7.8)		
	Other	15	13.1 (7.4)		
HADS (n = 71)	Normal	63	16.0 (5.7)	6.2 (1.8, 10.6)	0.006
	Abnormal	8	9.8 (6.8)		
* analysis of variance; only the p-value is presented.					

Where self-reported depression on HADS was recorded, there was evidence of an association with a raw SVF score ($p = 0.006$), and a higher incidence of high grade tumour ($n = 6$) and non-focal first symptom presentation ($n = 5$). However, as only 8 patients scored ≥ 8 points on HADS versus 63 patients scoring within the normal range, caution must be used when reporting this result.

MMSE and SVF correlations

Only 20 patients of 84 patients who were able to complete a MMSE had impaired test performance, as defined by an MMSE impairment cut-off score ≤ 26 [21,22] with 29 patients scoring a maximum of 30 (35%). Fourteen patients who were deemed as impaired on SVF (z-score ≤ -1.5 SD), scored above 26 points on the MMSE while 3 patients scored a maximum of 30 points probably suggesting MMSE has a ceiling effect.

A weighted Kappa was used to measure the level of agreement between MMSE and SVF impairment groups, which showed moderate agreement (weighted Kappa=0.53). Pearson's correlation revealed a positive 'moderate-to-strong' correlation between SVF and MMSE total scores ($r=0.591$, $n=84$, $p<0.0001$).

Discussion

This is the first study of pre-operative patients with brain tumour to show that there are differences in executive function performance, as assessed by a quick screening test such as the semantic verbal fluency test ("number of animals in one minute"), across different symptom presentations.

Over 75% of our patients scored below average of SVF test performance matched for age and education and 40% had impaired SVF performance, as defined by a mean below -1.5 SD relative to normative data. Adjusted SVF score was found to be lower for patients with headache or headache-plus symptoms compared to patients with focal neurological deficits or seizures. Of clinical relevance, where there are diagnostic uncertainties for the primary care clinician with respect to which patients with non-focal symptoms such as headache to refer urgently, low performance on the test may be another "red flag". The study was not designed to define a cut-off value in this patient population, which is a limitation of the study (discussed later).

Compared to MMSE, SVF is able to identify more patients with the presence of cognitive impairment [23] and does not suffer from a ceiling effect, which is observed with MMSE. The SVF test is faster to complete and more likely to be completed than the full MMSE or full ACE-R. There was a positive 'moderate-to-strong' correlation between MMSE and SVF.

While cognitive deficits are frequently demonstrated in brain tumour patients in the post-surgical interval [24–27], few studies to date examined it before surgery. Using a comprehensive neuropsychological battery, Tucha and colleagues [6] showed that nearly all patients (91%) with a newly diagnosed brain tumour prior to neurosurgical treatment displayed impairments in at least one area of cognition. Executive function and memory were the most frequently affected domains (78% and 64%, respectively). Talacchi [19] examined 29 patients with glioma before and after surgery. At baseline, 79% of patients demonstrated impaired cognition in at least one test with word fluency and verbal memory being one of the most frequently affected functions. The frequency of test impairment in our study was lower and is likely reflected by a different approach and the level set to define test impairment, for which a z-score was calculated, and by a limited formal cognitive assessment with one validated tool. Tucha and colleagues [6] employed an extensive battery of cognitive tests and defined test impairment if scores fell below the

10th percentile of normative data. There is, however, the probability of over-estimation of cognitive impairment with increasing numbers of tests used [6].

Evidence of objective poor performance in a simple test of speed of thinking such as the semantic verbal fluency test for animals, in patients with headache or “headache plus” is perhaps not surprising. In patients with known brain tumour, headache is likely to reflect a local intracranial mass effect, with or without raised intracranial pressure or hydrocephalus [6]. Previous studies have shown that cognitive symptoms frequently accompany brain tumour associated headache, although may be subtle and not be complained of by the patient. Semantic verbal fluency is likely to be affected in other intracranial conditions associated with headache (e.g. cerebral venous sinus thrombosis and subarachnoid haemorrhage) and is unlikely to be brain tumour specific. Subtle cognitive or personality changes may precede headache or development of focal neurological deficits [28]. Reduction in oedema was found to improve or prevent further deterioration of memory and word fluency in patients with high grade glioma (HGG) [19].

The fact that we did not find any evidence of significant differences in SVF scores and laterality of brain tumour may suggest that the SVF may indeed involve more widely distributed neuronal networks. This is supported by previous lesion research [29, 30]. Szatkowska [29] examined patients with right and left frontal lesions (tumour and aneurysms) on semantic fluency performance, laterality difference was not observed for semantic fluency.

Affective disorders can adversely influence cognitive performance in healthy population and brain tumour patients [31–34]. A systematic review of observational studies showed a consistently lower physical and cognitive functioning and reduced quality of life in glioma patients with depression [35]. Patients in the current study self-rated their level of depression on a widely used Hospital Anxiety and Depression Scale (HADS). Semantic verbal fluency performance was significantly lower for those with a higher level of depressive symptomatology (HADS score ≥ 8). However, patient size was small ($n = 8$) while most had an aggressive tumour. It does not, thus, permit to conclude that SVF result in the present study was confounded by mood. A consistent finding was reported by Robinson *et al* [36].

A limitation of this study is the absence of a control group of patients with primary headache. It may be argued that during headache there may be reduced cognitive reserve, but cognition should be normal between migraine episodes. Literature on the topic is inconsistent to date, with some smaller cross-sectional studies showing evidence of worse cognitive performance in people during migraine [37–40] while larger cross-sectional and longitudinal studies reporting the lack of any association in migraine or chronic tension-type headache sufferers [41–47]. Migraine is generally an episodic condition and no studies suggest a problem with cognition between attacks. To overcome this limitation, our group are currently conducting a study to examine SVF performance in patients with headache referred for a direct access brain imaging, to study semantic verbal fluency in those ultimately diagnosed as having migraine and those with headaches and an abnormal scan, including tumour.

The high frequency of impairment on SVF might reflect the later stages of their diagnostic disease pathway. It is thus possible that patients perform better at initial stages of the disease (first presentation to primary care). This would require employing SVF as a cognitive screening test for a large number of patients attending their primary care doctor with headache, during their first few consultations. We have introduced a headache suspicious of cancer, electronic protocol based referral for direct access imaging, which requires that the primary care clinician completes the SVF test to obtain a brain scan within 48 hours of referral, to further study this.

Where patients complain of cognitive symptoms it is not surprising that this fast objective screening test is abnormal. What is more clinically important is the presentation of patients with headache related to brain tumour, who do not complain of cognitive difficulty, the SVF test is frequently abnormal. Few younger patients in our sample complained of cognitive symptoms initially, yet the group's mean SVF score is 15.8 which is between the 10th and 25th centile of normative score [18]. It therefore raises a suspicion of under-recognition of mild initial cognitive deficits in younger patients who may themselves attribute it to stress or fatigue. Indeed, similar observation was reported previously [6].

Our study compared the association of SVF and MMSE in detecting cognitive impairment in brain tumour patients prior to surgical treatment. MMSE is the most widely used cognitive screening test in neuro-oncological practice [22] and in large clinical trials [22, 48]. Finding a positive 'moderate-to-strong' correlation between it and SVF, affirms the validity of SVF in this setting. The present study supports the general belief that MMSE has a lower detection rate of mild and/or focal brain tumour associated cognitive deficits such as abstract reasoning, executive functioning [22, 49], and if normal score is achieved, additional cognitive testing would be required.

Conclusions

Trying to identify which patients with headache to refer urgently for a scan or a specialist can be difficult. There will be a higher index of suspicion of cancer in older patients presenting with a new or rapidly progressive headache than younger patients with headache. Any other factors that might aid selection of patients with "headache only" for scanning and act as additional "red flags" for referral may be helpful in the primary care. Semantic verbal fluency test is a quick screening tool for executive function. If there is a poor performance on an objective test such as "number of animals in a minute", we would suggest this is included in the "headache plus" category, raising the suspicion of intracranial lesion causing cognitive problems. This, of course, needs to be correlated with relevant clinical information, taking into account patient's demographics, risk factors, symptomatology as well as doctor's clinical instinct.

Declarations

Ethics approval and consent to participate

This is a secondary analysis of a previously reported prospective observational study assessing patient's consent. Local research ethics committee (LREC) approval for the study was sought but deemed unnecessary by the LREC committee since the study was to assess capacity to consent to surgery, and no consent was necessary to enrol patients.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed in the current study are available from corresponding author on reasonable request.

Competing interests

Dr Zienius has no interests to disclose

Dr Kerrigan has no interests to disclose

Ms Tuck has no interests to disclose

Dr Grant has no interests to disclose

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Authors' contributions

Dr Zienius: data analysis and co-wrote the first draft of the paper

Dr Kerrigan: study concept, design and data acquisition

Ms Tuck: assistance with statistical analysis

Dr Grant: study design, analysis and co-wrote the first draft of the paper

All authors approved the final manuscript.

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