Article:

Article title: Cognitive deficits in vasculitis of the nervous system: A cross-sectional study

Running title: Cognitive deficits in vasculitis

Abstract

Objectives

To identify the cognitive and functional deficits in a well-characterized group of patients with vasculitis of the nervous system.

Methods

Sixty seven patients diagnosed with Central Nervous System (CNS) or Peripheral nervous System (PNS) vasculitis over a 14 year period were retrospectively identified. Data on clinical presentation, laboratory, radiographic and tissue biopsy investigations, and treatment, were collated. Cognitive, functional and quality of life evaluation assessments were performed in 31 patients who agreed to participate and included Addenbrooke's Cognitive Examination-revised (ACE-R), Nottingham Extended Activities of Daily Living (NEADL) and EQ-5D-3L quality of life questionnaires.

Results

CNS vasculitis patients exhibited cognitive impairment, with a mean ACE-R score of 74/100 (standard deviation (SD) 16). NEADL and EQ-5D-3L scores were in the impaired range at 41/66 (SD 21) and 57/81 (SD 22), respectively. Patients with just PNS vasculitis exhibited fewer cognitive deficits with ACE-R and NEADL scores of 87 (SD 8) and 46 (SD 16) respectively. EQ-5D-3L score was in the impaired range of 65 (SD 22).

Conclusions

Vasculitis of the nervous system and, in particular, CNS vasculitis causes cognitive impairment and deficits in functional ability. Such patients should be targeted for cognitive rehabilitation.

Key Words: CNS vasculitis, PNS vasculitis, angiitis of the CNS and PNS, cognitive decline, long term consequences, quality of life.

Introduction

Vasculitis refers to a group of disorders, with variable presentation, that are pathologically defined by inflammation of the arterial wall. Classification of vasculitis can be based on anatomical site (central nervous system-CNS, peripheral nervous system-PNS, renal, skin etc) [2], size of involved vessels (large, medium or small) and/or the aetiology (primary [4-6] or secondary [5-9] to a connective tissue disease, cancer, drugs or infection). Cerebral angiography (CA), is considered the "gold standard" [2] imaging modality for CNS vasculitis but can be false-negative in 20-30% of cases especially in those with small vessel involvement. Less invasive techniques, such as computerised tomographic angiography

(CTA) or magnetic resonance angiography (MRA) can also be used. MRA though, is preferred due to the absence of radiation and the additional information of brain involvement in the context of vasculitis.

In clinical practice the diagnosis is often based on detailed history and examination, ancillary investigations and exclusion of mimics. Diagnostic criteria by Calabrese and Mallek suggested that the following three conditions are met: neurological deficits cannot be attributed to any other condition, positive findings on cerebral angiogram and/or CNS or peripheral nerve biopsy and no evidence of any other disorder to which the angiographic or pathological clinical findings might be secondary [3]. The present study aims to investigate the direct cognitive impairments of nervous system vasculitis, and any differences between patients with CNS versus PNS vasculitis.

Materials and Methods

The study was approved by the North West–Greater Manchester Research Ethics Committee (14/NW/0213). We performed a retrospective review of all patients diagnosed with vasculitis at the Royal Hallamshire Hospital in a dedicated neuroimmunology/rheumatology clinic with expertise in the diagnosis and management of vasculitis between 2000 – 2014. All cases with available clinical data were included. Patients under active follow-up in 2014 were identified and asked to perform assessments of cognition, ability to execute everyday activities and quality of life using the revised Addenbrooke's Cognitive Examination (ACE-R) [14-16], Nottingham Extended Activities of Daily Living (NEADL) scale [17] and EQ-5D-3L questionnaire [18-20], respectively.

ACE-R is a bed side cognitive test that assesses five cognitive domains; attention/orientation, memory, verbal fluency, language and visuospatial abilities, with a total score of 100 and cut-off scores for detecting neurodegenerative dementia at 82.

NEADL test comprises of 22 questions categorized into four subclasses; mobility, kitchen, domestic, and leisure depicting the confidence in performing regular activities of everyday life. The maximum score is 66, higher scores are linked with better life quality and independence.

EQ-5D-3L includes a descriptive series of quality of life and general health condition statements relying on five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the categories can take one of three responses, which record three levels of severity (no problems/some or moderate problems/extreme problems). The maximum score is calculated on a scale of 100, with 81.3 the mean functional score during the 6th decade in healthy individuals.

One-tailed unpaired t-tests were used to compare outcomes between CNS vasculitis and PNS vasculitis patients. All statistical analysis was performed using Social Statistics Online Calculator. Statistical significance was considered at $p<0.05$ level.

Results

Complete clinical and demographic data were available on sixty- seven patients with nervous system vasculitis treated at the Neuroscience Department, Royal Hallamshire Hospital, Sheffield, UK between 2000 and 2014. Out of these 67 patients thirty-one consented to undergo cognitive assessments.

Clinical characteristics and investigations

Of the 67 patients 47 (62%) were females and 20 (38%) males. Forty-eight had CNS vasculitis (24 primary and 24 secondary vasculitis). Nineteen had PNS vasculitis (7 primary and 12 secondary vasculitis). The mean age for patients with CNS vasculitis was 52.8 years (24-84) and for patients with PNS vasculitis 62.2 years (38-86), with a mean age for the whole group of 58.5 years. In total, 31 patients had primary (46.2%) and 36 (53.8%) had secondary vasculitis.

Thirty-one out of 67 patients (46.2%) with CNS vasculitis complained of headache at presentation. Acute focal neurological deficit (stroke like episodes) and general malaise were the second most common symptoms (22 out of 67 patients, 32.8%).

Thirty-two percent of patients had isolated CNS vasculitis, 23% had Wegener's granulomatosis, 17% had isolated PNS vasculitis, 9% had giant cell vasculitis, 8% had small vessel vasculitis associated with P-ANCA (and elevated myeloperoxidase), 6% had vasculitis associated with systemic lupus erythematosus (SLE), 4% vasculitis associated with rheumatoid arthritis (RA) and 2% each with Churg-Strauss and vasculitis associated with Sjogren's syndrome.

Therapeutic interventions, for all patient groups, included steroids in 81%, mycophenolate 42%, cyclophosphamide 54%, and azathioprine 14%.

Neuroimaging (MRI, MRA, CT, CTA) identified vascular abnormalities in 75% of the patients with CNS vasculitis. In 65% of the cohort, the diagnosis was made without tissue biopsy.

One Consultant Neurologist and 2 Consultant Rheumatologists with extensive experience in the management of vasculitis were responsible for the diagnosis in this cohort

of patients. All patients were followed up in joint neurology/rheumatology clinics after initiation of treatment. The diagnosis was made using detail clinical history and examination together with laboratory tests, neuroimaging, angiography and neurophysiology. The presentation of CNS versus PNS vasculitis was very distinct. All patients with PNS vasculitis presented with symptoms and signs of peripheral nerve involvement (lower motor neuron findings with peripheral pain, weakness, areflexia and asymmetrical involvement typical of mononeuropathy multiplex-MMX). Neurophysiological assessment confirmed MMX in all patients with PNS vasculitis. Such patients underwent brain imaging only if they had symptoms of CNS involvement. By contrast, patients with CNS vasculitis presented with CNS involvement as outlined above. These patients would only undergo neurophysiological assessments if they had symptoms or signs of peripheral nervous system involvement.

Cognitive, functional and quality of life assessments

In total 31 patients completed an up-to-date cognitive assessment (21 with CNS and 10 with PNS vasculitis). Mean follow- up time (from diagnosis to cognitive assessment) was 53 months (range 3 days to 18 years). Their mean age was 56.1 years. Not all CNS and PNS vasculitis patients completed all three tests. The number of subjects that completed each assessment is specified in Table 1. Patients with CNS vasculitis exhibited cognitive impairment, with a mean ACE-R of 74/100 (standard deviation (SD) 16), below standard cut-off. NEADL and EQ-5D-3L scores were in the impaired range at 41/66 (SD 21) and 57/81 (SD 22), respectively (normal value EQ-5D-3L during the 6th decade of life 8.13)[18, 19, 20]. PNS patients exhibited less cognitive deficits with borderline normal ACE-R and NEADL scores of 87 (SD 8) and 46 (SD 16) respectively, but EQ-5D-3L score was in the impaired range of

65 (SD 22). The only significant difference between the two groups was in cognitive impairment (ACE-R).

[Table 1 near here]

Discussion

The key finding from this study is that patients with CNS and PNS vasculitis have significant residual deficits in cognition, daily function and quality of life, even after prolonged follow up. Cognitive impairment was significantly more in CNS rather than PNS vasculitis patients, consistent with the differing neuroanatomical disease targets. Self-reported function and quality of life measures were equally impaired in the two groups. This suggests that cognitive sequelae are not solely responsible for the impact on patients' lives. Prognosis must remain guarded and suggesting that ongoing support and cognitive rehabilitation is required. Patients with PNS vasculitis, as expected, were less cognitively affected, although they had reduced quality of life. This may be secondary to their physical disability including neuropathic pain and residual weakness.

Taking into consideration that the mean NEADL score for patients who experience atherosclerotic stroke is 32, an average score above 32, for both CNS and PNS [Table 1], suggests better quality of life for this cohort. CNS involvement may well have an impact on this self-reported parameter [17], so some caution in interpretation is required. A possible reason for this difference between patients with CNS vasculitis and patients with atherosclerotic stroke is the fact that stroke-like episodes in CNS vasculitis are often reversible if treated promptly, rarely recur and they affect a younger population (80% of patients with atherosclerotic stroke are older than 80 years) [33].

There was no significant difference in EQ-5D-3L scores between the CNS and PNS vasculitis groups. However, both groups scored lower than the age-adjusted scores [18-20], suggesting that both central and peripheral nervous system vasculitis affects quality of life.

Our findings that vasculitis patients have significant cognitive deficits are compatible with previous studies [10-13] supporting the theory that physical sequelae are not solely responsible for these deficits. Moreover, we offer evidence that, although the type of vasculitis may not influence quality of life, it does influence cognitive outcomes with those with CNS vasculitis most severely affected.

Cognitive impairment is a common symptom of CNS vasculitis [10-12] and has also been used as indicator of patients' response to treatment. There are a few studies of the long-term consequences of CNS vasculitis [10-11], which include case studies [12] and studies of vasculitis in association with other pathologies [13]. The two largest and most comprehensive studies [11-12] assessed patients with CNS vasculitis at 21 and 8 years respectively and reported their clinical progress and neuroimaging results. Both studies concluded that immunosuppressive therapy including corticosteroids improved physical and cognitive deficits. The long-term impairments in patients with CNS vasculitis are consistent with findings from previous studies [10-13] and are likely to contribute to the identified difficulties with daily living in this group. Salvarani et al conducted 21 years follow- up in 101 patients, and reported Rankin scores [10]. The scores at diagnosis were summed into three subgroups (0–2, no or light disability; 3, mild disability; 4–5, severe disability). The median duration of follow-up for the 101 patients was 13 months (range, 0–13.7 years). The majority of patients presenting low disability scores at initial diagnosis (Rankin score, 0–2; 57 patients) maintained them until last follow-up (Rankin score, 0–3). Most of the 22 patients initially within the serious disability range (Rankin score, 4–5) improved at follow-up (Rankin score, 0–3). Seventeen patients died during follow-up. Hubert de Boysson et al

assessed 112 patients over 8 years and reported similar findings [11]. Patients were categorized in three groups, depending on the therapeutic schema followed, and their initial mean Rankin score was 4. Improvement to most recent follow-up (Rankin score, ≤2) was observed in 63 (56%) patients. In another study [13], 11 patients with neuroborreliosis-related vasculitis were assessed using radiological, serological and immunological methods, but this group with an infective aetiology are likely to differ in characteristics to ours.

The limitations of this study include the small numbers, the risk of selection bias in patients consenting to undergo the assessments, and also the challenges of case ascertainment, common to all studies of CNS vasculitis. The small numbers meant that subgroup analysis (eg type of vasculitis, large versus small vessel disease etc) was not possible. It has been shown that when smaller vessels are affected, cognitive deficits are more profound [11]. CNS vasculitis is rare [2], the clinical features can be non-specific and diagnosis is often delayed unless the patients are managed by experienced physicians; a previous report found that diagnosis took 6 months from symptom onset in 75% of patients [21]. One other notable limitation is mortality. Our study reports 12% mortality, concordant with other studies that report ranges between 8-16%, for 8 and 21 years follow- up respectively, another barrier to long-term follow-up [10-11]. A final limitation is the absence of parallel healthy control subjects.

This study was not concerned with the means of diagnosing CNS or PNS vasculitis. The diagnosis in this cohort was based on the expertise of a neurologist and a rheumatologist with experience in the diagnosis and management of vasculitis [30]. The clinical diagnosis was supported by neuroimaging [22-29] and laboratory data, as described above. The favorable response to treatment and no emergence of alternative diagnoses on long-term clinical follow-up are also supportive of the correct diagnosis [31-32].

Cognitive rehabilitation tends to be neglected in the context of vasculitis, primarily because at presentation these patients are often extremely unwell but, in our experience, respond well once early diagnosis and instigation of effective treatment takes place. The often dramatic improvement of such patients at the initial stages of treatment may be a contributory factor to the failure to consider long term cognitive rehabilitation. The findings from this study suggest that this is an area that merits further consideration.

Conclusion

CNS vasculitis results in long-term cognitive impairment and both CNS and PNS vasculitis result in a decline in quality of life and impairment of activities of daily living. Both CNS and PNS vasculitis patients should be considered for rehabilitation strategies to help with long-term impairment of daily function and quality of life, and in CNS vasculitis patients, there may be a role for cognitive rehabilitation.

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