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Everyday cognitive failure in patients suffering from neurosarcoidosis

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Abstract. *Background:* Cognitive failure is associated with memory and concentration problems. Previously, a prevalence of one third was found in a general sarcoidosis population. The aim of this study was to assess if neurosarcoidosis patients are at higher risk for developing everyday cognitive failure using the Cognitive Failure Questionnaire (CFQ) and to determine what factors were associated with cognitive failure. *Methods:* A cross-sectional web-based survey was conducted from April to May 2017 in a national sample of neurosarcoidosis patients. The survey asked about complaints and included 3 questionnaires (Fatigue Assessment Scale [FAS], Small Fiber Neuropathy Screening List [SFNSL] and CFQ. Data were compared to a general sarcoidosis population. *Results:* Of the 152 patients who completed the survey, 131 had neurosarcoidosis. The mean CFQ score was significantly higher in the neurosarcoidosis (45.6±20.7) compared to the general sarcoidosis population (36.2±15.9; p< 0.0001). High CFQ scores (≥43) were found in 55.7% and 33.9%, respectively (p<0.0001). The FAS score (OR 21.4) and SFNSL score (OR 4.3) were the strongest positive predictors of a high CFQ score. *Conclusion:* Cognitive failure is a significant problem in neurosarcoidosis. More than half of the patients reported cognitive deficits, compared to one third of a general sarcoidosis population. Fatigue and small fiber neuropathy play a role in cognitive failure. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36: 2-10)*

Key words: neurosarcoidosis, cognitive failure, small fiber neuropathy (SFN), fatigue, sarcoidosis

Introduction

Cognitive failure is a cognitive error occurring during the performance of a task that a person would normally execute successfully in everyday life (1, 2). Cognitive failure is characterized by concentration problems, memory loss and decreased perception. It is associated with various disease entities, such as chronic obstructive pulmonary disease, obstructive sleep apnoea, chronic heart failure, rheumatoid arthritis, primary Sjögren syndrome, multiple sclerosis and sarcoidosis. Factors associated with a higher prevalence of cognitive failure in these different disease entities include fatigue, depression, pain due to small fiber neuropathy (SFN), microangiopathy, inflammatory molecules such as TNF-alpha, cerebrovascular disease and chronic hypoxia (1, 3-7).

Sarcoidosis is a multisystem inflammatory disorder of unknown etiology in genetically predisposed

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individuals, affecting 1-40 per 100 000 persons (8, 9). The natural history and prognosis of sarcoidosis are highly variable and its course is often unpredictable. Clinical manifestations vary, depending on the organs involved (10, 11). Involvement of the nervous system, neurosarcoidosis, is present in approximately 5% of the cases and has a heterogeneous clinical presentation, from chronic meningitis to myelopathy (12, 13).

Apart from organ-related symptoms, patients may suffer from a variety of nonspecific disabling symptoms that cannot be explained by granulomatous inflammation of an organ, such as fatigue and small fiber neuropathy (SFN) (14). Both have a high prevalence. Fatigue occurs in 50-85% of sarcoidosis patients (11, 15) and SFN in 40-60% (16, 17). In addition, Elfferich et al. found everyday cognitive failure in 35% of the cases they studied in a general sarcoidosis population (1). Cognitive failure has a great impact on the lives of sarcoidosis patients, since they are mostly young.

Broadbent et al. developed the Cognitive Failure Questionnaire (CFQ), a self-report questionnaire assessing failures in everyday errors of attention, perception, memory and motor function (2). In general, the CFQ appears to be a reliable and brief measure useful in clinical practice.

We hypothesized that everyday cognitive functioning may be even more impaired in patients with neurosarcoidosis. The aim of this study was therefore to examine the prevalence of everyday cognitive failure using the CFQ in patients suffering from neurosarcoidosis compared to a general sarcoidosis population. We also studied what factors were associated with cognitive failure.

Methods

Study design

A cross-sectional web-based anonymous survey was conducted from April to May 2017 among a national sample of neurosarcoidosis patients (Group I). The recruitment procedure aimed to compose a representative sample of neurosarcoidosis patients in the Netherlands. Data from the study by Elfferich et al., performed in a general sarcoidosis population (n=343) served as a control group for comparisons of the scores on the CFQ, the small fiber neuropathy screening list [SFNSL], and the fatigue assessment scale [FAS] (1). This latter population was subdivided in those without neurosarcoidosis (Group II, n=330) and those with neurosarcoidosis (Group III, n=13).

This study was performed in accordance with the Declaration of Helsinki and its amendments. The Medical Ethics Committee of the St. Antonius Hospital Nieuwegein, The Netherlands, decided that, under the Dutch act on medical research involving human subjects, approval of this study by a Medical Ethics Committee was not necessary.

Study sample and procedure

The overall study sample (group I) comprised patients from our online Dutch Neurosarcoidosis Registry and neurosarcoidosis patients from the Dutch Sarcoidosis Society. The diagnosis of neurosarcoidosis was confirmed for each of the patients by a neurologist, using the Zajicek or Marangoni (modified Zajicek) criteria, labelling patients as possible, probable or definite neurosarcoidosis (18, 19). SFN was classified as 'paraneurosarcoidosis', since the hallmark of sarcoidosis (granuloma formation) is not found in the small fibers (20-23). Patients suffering solely from SFN were therefore excluded from this study.

All patients included in the Dutch Neurosarcoidosis Registry have agreed to participate in online research studies. Patients from the Dutch Sarcoidosis Society (Sarcoidose.nl) were recruited without incentives, since the survey was anonymous. There was no overlap in registrations between the two sources. All patients had sufficient command of Dutch and had access to the internet.

A survey was developed using the online questionnaire tool *Surveymonkey* (www.surveymonkey.com). The survey included self-reported complaints, sarcoidosis manifestations, demographics (gender, age, duration of sarcoidosis), use of medication, daily impairments and a set of questionnaires validated for sarcoidosis, the CFQ (2), the SFNSL (24) and the FAS (25). An invitation to complete the electronic survey was sent by email to all the patients in our online Dutch Neurosarcoidosis Registry. Additional patients were recruited by means of an advertisement on the website of the Dutch Sarcoidosis Society, Sarcoidose.nl, providing a link to the electronic sur-

vey. Of the 153 patients who started the survey, 152 (99%) completed it.

Questionnaires

In the sarcoidosis population, so far no questionnaires regarding evaluation of cognitive failure are validated. Broadbent et al. developed the CFQ to evaluate cognitive failure, which appears to be a brief and reliable questionnaire that is useful in clinical practice. Since this questionnaire was previously used to evaluate cognitive failure in the general sarcoidosis population, we decided to also use the CFQ in the neurosarcoidosis population (1). The CFQ is a self-report questionnaire consisting of 25 items assessing deficits regarding attention, perception, memory and motor functioning in everyday life. The total CFQ score is calculated by summation of all answers and scores range from 0-100. A higher total score indicates more subjective cognitive failure. A high CFQ score is defined as a score ≥43 (mean of the controls plus one standard deviation) (2).

The FAS is a 10-item self-report fatigue questionnaire. In addition to the total fatigue score, the FAS yields a mental fatigue score and a physical fatigue score. The response scale is a five-point scale (1 never to 5 always); scores on the FAS can range from 10 to 50. A score >22 indicates fatigue and a score >34 indicates extreme fatigue. The reliability and validity of the FAS have been shown to be good in sarcoidosis patients (25).

The SFNSL is a 21-item self-administered questionnaire to screen for symptoms related to small fiber neuropathy (SFN). The response scale is a five-point scale (0 never to 4 always); scores on the SFNSL can range from 0 to 84. The cut-off score of the SFNSL is 11: a score below 11 indicates no or few symptoms related to SFN, while a score of 11-48 indicates probable or highly probable SFN and a score above 48 is indicative of SFN (24).

Statistical analysis

All statistical analyses were performed using SPSS version 24 for Mac. Standard descriptive statistics were computed. The chi-square test and Student t-test were used to test for statistically significant differences between two groups of neurosarcoidosis patients (i.e. those with CFQ <43 and those with CFQ ≥43). Chi-square tests were also performed to assess the prevalence (%) of cognitive failure (CFQ) in patients with neurosarcoidosis compared to a general sarcoidosis population. ANOVA was used for comparison between the general sarcoidosis population and the neurosarcoidosis population. Pearson correlations were calculated to evaluate the association between the CFQ scores and fatigue (FAS scores) as well as symptoms suggestive of SFN (SFNSL scores). Multivariate logistic regression analyses were used to assess the influence of the FAS scores and SFNSL scores on the CFQ scores, after adjustment for age, sex, treatment, depressive symptoms and sleeping disturbances. Because of the large number of correlations examined, a probability value of less than 0.01 was considered to be statistically significant.

Results

A total of 152 patients (99%) completed the survey. Neurosarcoidosis had been established in 131 patients (86.2%), 12 patients did not have neurosarcoidosis, and in 9 cases the diagnosis remained unclear. Finally, therefore, 131 patients suffering from neurosarcoidosis were included in this study. The studied population is approximately 25% of the estimated total neurosarcoidosis population in the Netherlands. The various neurosarcoidosis manifestations in the studied population were cranial nerve palsy (45.1%), spinal cord involvement (29.4%), chronic meningitis (26.5%), cerebral involvement (20.6%), peripheral neuropathy (15.7%), myelitis (9.8%), neuro-endocrine involvement (9.8%), hydrocephalus (6.9%), brainstem involvement (4.9%), and cerebral vascular involvement (3.9%). Almost half of the population had multiple manifestations (45%). Demographic and clinical data are summarized in table 1.

The mean CFQ score in the neurosarcoidosis population we studied was 45.6±20.7. There were no significant differences between the subgroup with a high CFQ score and the subgroup with a normal CFQ score as regards sex, age, time since diagnosis, or medication use. Pain, pulmonary symptoms (cough and dyspnea), self-reported depressive symptoms and self-reported sleeping disturbances were

Table 1. Summary of the characteristics of the studied neurosarcoidosis population subdivided into those with normal Cognitive Failure Questionnaire (CFQ) scores and those with high CFQ scores

	Total	CFQ < 43	CFQ ≥43	p-values#
Patients, n (%)	131	58 (44.3)	73 (55.7)	-
Sex (male:female), n (%)	67(51.1): 64 (48.9)	27(46.6): 31 (53.4)	40 (54.8): 33 (45.2)	0.349
Age, years (range)	51.9±10.4 (21-75)	52.8±11 (21-75)	51.4±10.0 (28-74)	0.444
Time since diagnosis, years (range)	8.7±7.2 (0-35)	8.0±6.7 (0-35)	9.3±7.6(1-35)	0.292
Symptoms				
- Pain, n (%)	92 (70.2)	32 (55.2)	60 (82.2)	0.001
- Cough and dyspnea, n (%)	30 (22.9)	5 (8.6)	25 (34.2)	0.001
- Ocular, n (%)	57 (43.5)	21 (36.2)	36 (49.3)	0.133
- Cardiac, n (%)	9 (6.9)	4 (6.9)	5 (6.8)	0.992
- Skin, n (%)	48 (33.6)	15 (25.9)	31 (42.5)	0.048
- Joint, n (%)	89 (67.9)	33 (56.9)	56 (76.7)	0.016
- Hypercalcemia, n (%)	9 (6.9)	2 (3.4)	7 (9.6)	0.168
- Kidney stones, n (%)	3 (2.3)	0 (0)	3 (4.1)	0.118
Medication use				
- never, n (%)	26 (24.4)	12 (20.7)	14 (19.2)	0.829
- first line treatment, n (%) (prednisone or dexamethasone)	99 (75.6)	43 (74.1)	56 (76.7)	0.733
- second line treatment, n (%) (methotrexate azathioprine, mycolfenolate mofetyl)	50 (38.2)	20 (34.5)	30 (41.1)	0.439
- third line treatment, n (%) (anti-TNF-alpha: adalimumab, infliximab)	22 (16.8)	10 (17.2)	12 (16.4)	0.903
Psychological variables				
Self-reported				
Depressive symptoms	33 (25.2)	8 (13.8)	25 (34.2)	0.007
Sleeping disturbances	70 (53.4)	18 (31)	52 (71.2)	<0.0001
Questionnaires				
CFQ score	45.6±20.7	27.0±10.9	60.3±13.4	<0.0001
FAS total score	34.8±8.0	30.2±7.8	38.5±6.3	<0.0001*
- FAS-score <22, n (%)	10 (7.6)	9 (15.5)	1 (1.4)	
- FAS-score 22-34, n (%)	51 (38.9)	33 (56.9)	18 (24.7)	
- FAS-score >34, n (%)	70 (53.4)	16 (27.6)	54 (74)	
FAS mental score	15.8±4.4	13.5±4.0	17.6±3.9	<0.0001
FAS physical score	19.0±4.1	16.7±4.1	20.8±2.9	<0.0001
SFNSL score	39.7±21.3	29.0±18.9	48.3±19.3	<0.0001*
- SFNSL score <11, n (%)	11 (8.4)	10 (17.2)	1 (1.4)	
- SFNSL score 11-48, n (%)	69 (52.7)	38 (65.5)	31 (42.5)	
- SFNSL score >48, n (%)	51 (38.9)	10 (17.2)	41 (56.2)	

Data are expressed as means ± SD, n=absolute number or percentages. # p-value CFQ <43 vs CFQ ≥43, *p-value for total and subscores. CFQ=Cognitive Failure Questionnaire, FAS=Fatigue Assessment Scale, SFNSL=Small Fiber Neuropathy Screening List

more prevalent in the group with a high CFQ score (see table 1).

The prevalence of a high CFQ score in the neurosarcoidosis sample (55.7%) was significantly higher than in the general sarcoidosis population studied by Elfferich (n=330, 33.9%, p<0.0001; see table 2) and comparable with the results in a subgroup of neurosarcoidosis patients (n=13) in the study by Elfferich et al. (55.7% versus 53.8%) (1).

Almost all neurosarcoidosis patients in our study reported fatigue (n=121; 92.4%), 53.4% of whom experienced extreme fatigue (see table 1). Fatigue was more prevalent in neurosarcoidosis patients with a high CFQ score (98.6% vs 84.5%, respectively; p=<0.0001). The average FAS scores were also higher in neurosarcoidosis with a high CFQ score (38.5 vs 30.2, respectively; p=<0.0001) The overall FAS scores, as well as the FAS scores in the

high CFQ score subgroup, were significantly higher in the neurosarcoidosis population compared to the general sarcoidosis population (see table 2). Symptoms suggestive of SFN (SFNSL score >11) were significantly more prevalent in the neurosarcoidosis patients with a high CFQ score (98.6% vs 82.8%, respectively; p=<0.0001). Comparison with the data of the general sarcoidosis population showed that the SFNSL scores in our study sample were comparable to those in the general sarcoidosis population and the high CFQ score subgroup (see table 2).

No statistically significant differences were found between the neurosarcoidosis sample we studied (Group I) and the subgroup of neurosarcoidosis patients included in the study by Elfferich et al. (Group III) (1) as regards overall FAS, SFNSL and CFQ scores (data not shown). The average disease duration in our sample showed no statistically significant difference compared to the population of Elfferich. Disease duration did not influence everyday cognitive failure in sarcoidosis in this latter population and the population of the present study.

Correlation of FAS, SFNSL and CFQ

In our neurosarcoidosis population, both fatigue and SFNSL scores correlated significantly with the CFQ. The FAS scores showed the strongest correlation with the CFQ (R=0.65; see table 3). Patients with extreme fatigue (>34) appeared to be more at risk of developing cognitive failure than patients with a fatigue score >22 (R=0.46 vs R=0.27 respectively; p=<0.0001). Patients suffering from SFN related symptoms reported high CFQ scores (R=0.40, p=<0.0001).

Fatigue (OR 13.2) and symptoms suggestive of SFN (OR 5.5) were the strongest predictors of a high CFQ score. The OR of the SFNSL decreased after correction for sex, age, treatment, depressive symptoms and sleeping disturbances (OR 4.3, p<0.0001,

Table 2. Scores on the Cognitive Failure Questionnaire (CFQ), Fatigue Assessment Scale (FAS), Small Fiber Neuropathy Screening List (SFNSL), gender and age of the neurosarcoidosis sample studied (Group I) and a general sarcoidosis patient population without neurosarcoidosis (Group II) (1)

	Group I	Group II	p value
Patients n	131	330	
Gender : female %	48.9	44.8	NS
Age, years (range)	52.0±10.4 (21-75)	48.6±0.9 (25-79)	NS
FAS score total group	34.8 ± 8.0	29.2 ± 8.4	0.01
FAS total score in CFQ ≥43	38.5 ± 6.3	30.4 ± 12.1	0.001
SFNSL score total group	39.7 ± 21.3	42.4 ± 16.8	NS
SFNSL score in CFQ ≥43	48.3 ± 19.3	48.2 ± 16.8	NS
CFQ score	45.6 ± 20.7	36.2 ± 15.9	<0.0001
CFQ score ≥ 43, n (%)	73 (55.7)	112 (33.9)	<0.0001

Data are expressed as means ± SD, absolute number (n) or percentages (%). NS=not significant.

Table 3. Correlation of the scores on the Fatigue Assessment Scale (FAS) and Small Fiber Neuropathy (SFN) Screening List (SFNSL) with the Cognitive Failure Questionnaire (CFQ)

CFQ scores	FAS scores: total	FAS scores: mental	FAS scores: physical	SFNSL scores
Correlation (R=)	0.65	0.60	0.64	0.53
Significance (p-value)	<0.0001	<0.0001	<0.0001	<0.0001
CFQ scores		FAS scores >22: fatigue	FAS scores >34: extreme fatigue	SFNSL scores > 48: highly likely SFN
Correlation (R=)		0.27	0.46	0.40
Significance (p-value)		0.002	<0.0001	<0.0001

Table 4 Multivariate logistic regression Fatigue Assessment Scale (FAS) and Small Fiber Neuropathy Screening List (SFNSL) scores on the Cognitive Failure Questionnaire (CFQ) scores

	OR	95% CI	p-value
SFNSL	4.3	2-11.3	<0.0001
- Sleeping disturbances	3.9	1.7-8.6	0.001
FAS	21.4	2-225.2	0.011
- Age	0.34	0.1-0.8	0.016
- Gender	0.4	0.2-1	0.048
- Sleeping disturbances	5.3	2.4-12	<0.0001

OR = odds ratio, 95% CI = 95% confidence interval

CI 2.7-11.3), while the OR of the FAS increased (OR 21.4, p=0.011, CI 2.0-225.2) (see table 4).

Discussion

To the best of our knowledge, this was the first study to examine everyday cognitive functioning in patients suffering from neurosarcoidosis and to compare this with a general sarcoidosis population using the CFQ. We found that everyday cognitive failure was a significant problem in the neurosarcoidosis sample. More than half of the patients in our sample reported cognitive deficits, compared to one-third of a general sarcoidosis population studied by Elfferich et al. (1). Fatigue and symptoms of SFN were the most important predictors of cognitive failure.

Previously, it was demonstrated by Elfferich et al. that everyday cognitive failure is a substantial problem in sarcoidosis patients (1). In this latter study, no relation was found between the CFQ scores and inflammatory parameters, lung function test results, chest X-ray stages, sleeping problems nor dyspnea. Moreover, no differences regarding these mentioned clinical data were shown between those patients with a high or normal CFQ score. In line with the latter study, the strongest predictor of cognitive failure in neurosarcoidosis was fatigue. Fatigue has been reported in 50-85% of chronic sarcoidosis patients (11, 15) and is also associated with poorer cognitive performance (1). Almost all our neurosarcoidosis patients experienced fatigue (FAS ≥22), a higher proportion than in the general sarcoidosis population (80.6%) studied by Elfferich et al. (1). Among the patients with cognitive failure, the neurosarcoidosis patients experienced more fatigue than sarcoidosis patients presenting with other manifestations. Fatigue in neurosarcoidosis patients has previously been described to affect cognitive control (26). In a study comparing non-fatigued and fatigued participants, the fatigued participants had compromised executive control (27). Studies in colorectal and breast cancer also found fatigue to be associated with perceived cognitive failure (28, 29). Moreover, fatigue negatively affects cognitive performance, in particular response inhibition. It may induce overactivation of the visual cortex, which is related to impaired cognitive performance (30). We did not find a difference between mental or physical fatigue: both were equally associated with cognitive failure in neurosarcoidosis patients.

SFN was also a predictor of cognitive failure, although to a lesser extent. The reported prevalence of SFN varies from 40 to 60% (16, 17), and has been associated with poorer cognitive performance in a general sarcoidosis population (1). SFN was even more prevalent in the neurosarcoidosis patient population we studied (91.6%). One of the main symptoms of SFN is neuropathic pain. Previous studies have reported an association between chronic pain and cognitive deficits, including attention, working memory and executive function (31, 32). A study of primary Sjögren's patients with SFN found a correlation between the intensity of pain and the performance of executive functions (6). Hendriks et al. found that everyday cognitive failure, and symptoms suggestive of SFN, appeared to be significant predictors of fatigue (33). Moreover, they also found that cognitive failure and depression are the most important predictors of high levels of fatigue (33). The study of Bosse-Henck et al. also determined depression, anxiety, muscle pain and severity of dyspnea were predictors of the development of severe fatigue (34). In line with this, we found a higher prevalence of depressive symptoms but also sleeping disturbances in neurosarcoidosis patients with cognitive failure correlating with the higher prevalence of fatigue. Moreover, sleeping disturbances are also associated with fatigue, depressive symptoms, anxiety, and dyspnea (35, 36).

Cognition seems to be - at least partly - a consequence of fatigue and SFN in (neuro)sarcoidosis or due to a common underlying mechanism explaining the strong correlation between cognition, fatigue

and SFN. In a pilot study by our group, standard neuropsychological tests were used to assess the cognitive domains of memory sensorimotor speed, information processing speed and cognitive flexibility. Only a small number of sarcoidosis patients (n=27; 63% female; age 47.2±10.8 years) were tested and compared with healthy controls. They found that cognitive failure did not imply cognitive impairment (33). Thus, subjective cognitive failure was not associated with cognitive impairment. The latter study exemplifies the difficulties of the diagnostic classification of cognitive deficits in patients suffering from sarcoidosis without major morphological lesions, and emphasizes the necessity for further research in this field. Insight into cognitive functioning is of great importance to optimise the self-management skills of patients with sarcoidosis. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment. Although cognitive dysfunction is a core feature of (neuro)sarcoidosis, most currently available treatments do not address cognition (1). Although treatment should first focus on treating sarcoidosis and its activity (1), alternatives could be considered if this is not effective.

The hallmark of sarcoidosis is granulomatous inflammation, which is predominantly a T-helper 1 immune response mediated by lymphocytes, macrophages and cytokines such as tumor necrosis factor alpha (TNF-alpha) and interleukins (IL) (37). It has been suggested that alterations in these immunological parameters can affect psychomotor functions. Research in mice has shown that TNF-alpha is essential for the normal functioning of memory and learning and that overexpression of TNF-alpha leads to cognitive failure, so TNF-alpha seems to have both neuroprotective and neurodegenerative effects (38, 39). Previous research has demonstrated that TNF-alpha inhibition in a sarcoidosis population was the only treatment achieving improvement of CFQ scores (1). Thus, overexpression of TNF-alpha in the pathogenesis of fatigue and cognitive failure could explain the favourable effect of anti-TNF treatment in sarcoidosis patients on cognition and fatigue (1).

The management of sarcoidosis patients with fatigue and low energy levels should focus on the increased burden of concomitant symptoms. Since fatigue usually has a multifactorial cause, risk factors should also be examined and treated in combination (14, 34). Future research involving more comprehensive neuropsychological batteries is warranted to investigate psychological functioning and fatigue in sarcoidosis. In addition, further research should give more attention to possible mediating or confounding pathways and associations between everyday cognitive functioning, fatigue and SFN-related symptoms.

Limitations of this study

Our study was a cross-sectional study, in which the neuropsychological assessment of cognitive dysfunctions was restricted to a rather general and subjective screening instrument, the CFQ. It provides an impression of the prevalence and related factors. Labelling oneself as absent-minded or forgetful depends upon the perceived discrepancy between the subject's everyday memory functioning and her or his everyday memory demands. Self-reported cognitive changes or decline do not necessarily reflect actual cognitive decline, since subjective failure was not associated with cognitive impairment (33). Beliefs about cognitive changes are strongly influenced by self-efficacy beliefs, personality, vitality, the experience of daily functioning and coping styles. Nevertheless, it seems unlikely that the favourable effect on cognitive functioning reported by patients treated with anti-TNF-α drugs is attributable to the use of a subjective screening instrument (1). Despite being subjective, therefore, this is the first sign that everyday cognitive failure is a major problem in neurosarcoidosis patients.

Response bias cannot be excluded due to the recruitment procedure, e.g. voluntary participation. Nevertheless, the response rate was high (99%). The sample we studied is approximately 25% of the estimated total neurosarcoidosis population in the Netherlands, and therefore a rather representative reflection of this population.

Since neurosarcoidosis is a rare disorder with a great diversity of manifestations (with overlapping manifestations in 45% of cases), phenotyping aiming to perform statistical analysis would not have been valid or feasible due to the rather small sample sizes for each of the manifestations, unfortunately. However, it might be interesting to consider whether central neurological manifestations for instance expose more cognitive failure than peripheral ones.

Conclusion

Sarcoidosis patients, especially neurosarcoidosis patients, are at increased risk for developing everyday cognitive failure. More than half of the patients reported cognitive deficits, compared to one-third of a general sarcoidosis population. Cognitive problems in a relatively young patient population have a great impact on daily functioning and can lead to problems at work and in social life, leading to decreased quality of life. Fatigue and symptoms suggestive of small fiber neuropathy were the most important predictors of cognitive failure. Our study points towards the necessity to integrate the growing body of knowledge about neuropsychological deficits in sarcoidosis in the management of this disease, especially for those patients suffering from neurosarcoidosis. Further studies, including imaging and biomarkers, in furthering our understanding of cognitive failure in sarcoidosis are needed to determine the relationship between cognition, fatigue, sleepiness and small fiber neuropathy in sarcoidosis, and whether they might have a common pathogenesis.

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