Executive functions in sarcoidosis: a neurocognitive assessment study

Özgür Bilgin Topçuoğlu1, M. Kavas1, Hande Alibaş2, Gülgün Çetintaş Afşar3, Sibel Arınç3, İpek Midi2, Neşe Tuncer Elmacı1

1 Department of Neurology, Süreyyapaşa Chest Diseases and Thorax Surgery Training and Research Hospital, Maltepe, Istanbul, Turkey; 2 Department of Neurology, Marmara University School of Medicine, Üsküdar, Pendik, Istanbul, Turkey; 3 Department of Chest Diseases, Süreyyapaşa Chest Diseases and Thorax Surgery Training and Research Hospital, Maltepe, Istanbul, Turkey

Abstract. Background: Sarcoidosis is a multisystem, inflammatory disease characterized by non-caseating granulomas in multiple organs. Neuropsychological impairment has been told to be present in about 10% of sarcoidosis patients with diagnosed central nervous system (CNS) involvement. Both anatomical lesions and changes in immunological parameters in sarcoidosis may cause cognitive impairment. Based on the information that soluble interleukin-2 receptors (sIL-2R) and tumour necrosis factor alpha (TNF-α) which plays a role in the pathogenesis of sarcoidosis accumulate in the basal ganglia and prefrontal structures, impairment in executive functioning is most likely to be expected in sarcoidosis. In this study we aimed to evaluate executive functions in sarcoidosis patients. Method: This study included 21 sarcoidosis patients (14 females, 7 males) and 21 healthy controls (12 females, 9 males). All participants were given Beck Depression Inventory- Second Edition, Stroop Test, Verbal Fluency Tests, Digitspan Forward Test, Digitspan Backwards Test and Trail Making Test Part- B. Test results of sarcoidosis patients were compared with healthy controls. Results: No significant difference was detected between sarcoidosis patients and healthy controls by means of neuropsychological assessment tests (p>0.05). Conclusion: Our study showed that sarcoidosis patients did not have impairment in executive functions. This result may be commented in two different outcomes. One of them, would be the probable necessity of additional electrophysiological or radiological tests including detailed paradigms for evaluation of executive functions. Secondly the effect of therapeutics used in sarcoidosis (steroids and/or immunosuppressants) on cognition should be questioned regarding the controversial previous data which released cognitive decline in sarcoidosis. (Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 26-34)

Key words: sarcoidosis, executive functions, neurocognitive assessment

Introduction

Sarcoidosis or with its less common name Besnier- Boeck- Schaumann disease has been described by the three scientists who gave the disease their names in the late 1800s and early 1900s (1). It is a multisystem, inflammatory disease characterized by non-caseating granulomas in multiple organs, mainly in lungs (2).

Neurological involvement is defined to be present in 5%-10% of sarcoidosis patients (3).

Among neurological complaints, sarcoidosis patients not rarely mention about concentration problems, attention deficits and other mental problems. Neuropsychological impairment has been told to be present in about 10% of sarcoidosis patients with di-
agnosed central nervous system (CNS) involvement (4). Not only the parenchymal lesions caused by the disease itself but also changes in immunological parameters acting in neurosarcoidosis are known to affect neurocognitive processes (5).

Cognitive symptoms in sarcoidosis even though mentioned among neurological manifestations (6) have not been specified, so far. Except for the limited number of case reports mentioning decline in neurocognitive processes in neurosarcoidosis (NS) patients (7) any specific neuropsychological studies have not been performed.

Executive functioning which is among cognitive processes includes inhibition, selective and sustained attention, attention shifting, planning, problem solving and decision making (8) which work together to help us organize our actions towards a target. Executive functions are mediated by the frontal lobe and mainly the prefrontal cortex (dorsolateral prefrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex and orbitofrontal cortex) (9). Based on the information that soluble interleukin-2 receptors (sIL-2R) and tumour necrosis factor alpha (TNF-α) which play role in the pathogenesis of sarcoidosis accumulate in the basal ganglia and prefrontal structures (10-12), impairment in executive functioning is most likely to be expected in sarcoidosis patients.

We hypothesize that a sarcoidosis patient is affected by the immunological reaction and inflammation which still remains as the main theory in sarcoidosis pathogenesis (13) from the first day on. For this reason, we intended to examine executive functions of sarcoidosis patients before diagnosis of NS. Besides, the ambiguity of diagnosis of NS which still has not been firmly determined and requires mainly a clinical presentation suggestive of NS and exclusion of other diagnoses (14) encouraged our supposition.

In this study we aimed to evaluate executive functions in sarcoidosis patients without diagnosis of NS in order to demonstrate possible cognitive decline casued by the sarcoidosis pathogenesis itself in the early course which means before treatment with steroids or immunosupressants. Neurological features of sarcoidosis are already known to occur in the early course of the disease (3).

To our knowledge, this is the first study which focuses on executive functions in sarcoidosis patients without neurological involvement.

**METHODS**

**Patients**

For the purpose of this study, we performed a data search to identify sarcoidosis patients in the database of sarcoidosis outpatient clinic in Süreyyapaşa Chest Diseases and Thorax Surgery Training and Research Hospital, Istanbul. A total of 289 patients were first identified. Patients were diagnosed via lung biopsy and staged according to their clinical findings and pulmonary X-rays (Box 1) (15) by the same 2 chest diseases specialists following Scadding criteria: Patients with a normal chest X-ray were accepted as stage 0. Bilateral hilar lymphadenopathy without parenchymal infiltration was described as stage 1 while bilateral hilar lymphadenopathy with parenchymal infiltration was described as stage 2. Isolated parenchymal infiltration without lymphadenopathy was defined as stage 3. Parenchymal fibrosis presenting with fibrotic bands, bullae, hilar retraction, bronchiectasis and diaphragmatic tenting was described as stage 4 (16). Patients with diagnoses of NS or with prior neurological diagnoses that may interfere with neuropsychological findings (dementia, epilepsy, cerebrovascular diseases, neurocognitive diseases, neurodegenerative diseases), patients with comorbid psychiatric diseases, rather than depression according to DSM-IV TR or patients under medications for sarcoidosis and/or other medical conditions that may alter neuropsychological assessment like steroids and immunosupressants or antipsychotics were excluded. By excluding patients under steroids or

| Box 1. Sarcoidosis staging according to pulmonary X-ray findings (15) |
|-------------------------|---------------------|---------------------|
| X-Ray stage | Radiological finding | % at diagnosis |
| Stage 0 | Normal chest graphy | 5-15 |
| Stage 1 | Bilateral hilar lymphadenopathy | 45-65 |
| Stage 2 | Bilateral hilar lymphadenopathy with parenchymal infiltration | 30-40 |
| Stage 3 | Only parenchymal infiltration | 10-15 |
| Stage 4 | Parenchymal fibrosis | 5 |
immunosuppressant therapy, patients comprising stage 4 were eliminated. Further exclusion criteria were mental retardation, having loss of vision or hearing, color blindness, poor knowledge of Turkish language and illiteracy. Educational level of patients were regarded as years which they attended a formal education. Patients with cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) interpretation were selected for the study.

Twenty-one patients (Group I) between 18 and 65 years old who fulfilled the criteria were included in the study. Patients were divided into subgroups according to the presence of EEG abnormalities and MRI lesions. Patients with EEG abnormalities (Group IA) were compared to patients with normal EEG (Group IB) while patients with MRI lesions (Group IX) were compared to patients with normal MRI (Group IY). Another division was performed according to disease duration. Patients suffering from sarcoidosis for less than 24 months (Group Iα) were compared to patients suffering from sarcoidosis for more than 24 months (Group Iβ).

Healthy controls

Twenty-one healthy subjects (Group II) matching age, sex and educational level of the patients, who met the inclusion criteria while being apart from exclusion criteria were included in the study as healthy controls.

Ethical Approval

Institutional Ethics Committee of Marmara University, School of Medicine, provided approval for this study. All study participants provided a written informed consent.

Neuropsychological Assessment

All neuropsychological assessment tests were applied to the study groups by the same neurologist under supervision of Marmara University, Department of Neurology, Cognitive Neurology section.

Beck Depression Inventory-Second Edition (BDI-II) (17) was used to detect depressive symptoms. Patients were given a 21-question self-report, multiple choice questionnaire. Each question was regarded with a point according to the answer chosen. Overall points were calculated. Zero to 10 points were regarded as normal, 10 to 16 points demonstrated mild depressive symptoms while 17-29 points showed moderate depressive symptoms and 30-63 points reflected severe depressive symptoms.

Stroop Test (ST) was used to measure selective attention and cognitive flexibility (18, 19). ST was applied with 4 cards in 5 domains. First domain (ST1) was formed of names of colors printed in black ink. Participants were asked to read the written words (names of colors written in black ink). Second domain (ST2) was formed of names of colors printed in colored ink. Participants were asked to read the words (names of colors written in different colored ink). Third domain (ST3) was formed of colored ball figures. Participants were asked to name the color of the balls. Fourth domain (ST4) was formed of colored neutral words (words rather than names of colors). Participants were asked to name the color of the words (the color of the ink, in which the word (color name) is written, not to read the word itself). Each domain was evaluated by the time taken to finish the test, number of mistakes and number of corrections.

Verbal Fluency Tests (Controlled Word Association Test (CWAT) and Category Fluency Test (CFT) were used to assess language ability (20). In CWAT, participants were asked to name as many animal names as they can within 60 seconds. The number of correct words were calculated. In CFT, the participants were asked to produce as many words rather than human and city names as they can, starting with the letters K,A,S consecutively in 60 seconds each. All the number of correct words produced were added to each other and the overall point was calculated. In both tests, repeated words were regarded as perseverations and marked.

Digit Span Forward Test (DF) was used to evaluate attention and short-term memory and Digit Span Backwards Test (DB) was used to measure working memory (21, 22). In DF, the participants were asked to listen carefully to numbers which the physician says and try to remember them because they would be asked to repeat them in order when the physician finishes. The first series was composed of 2 different three -digits numbers and ended in 2 different seven -digit numbers series. When a partici-
pant repeated at least one of the three-digit numbers, he passed through a four-digit number test. The last number of digits, which the participant correctly repeated was regarded as the point he got from the test. In DB, in the first series 2 different two-digit numbers were read and the participant was asked to repeat the digits backwards. Similarly with DF, the participant passed to a higher series when he correctly repeated at least one number from the former series. The last number of digits, which the participant correctly repeated was regarded as the point he got from the test.

Trail Making Test Part B (TMB) was used to assess processing speed and interference control (23). TMB consisted of connecting a set of numbers in order and a set of letters in alphabetical order by alternating between numbers and letters. The participant started with 1 in numbers followed by the letter A and asked to continue alternating up to 13 in numbers and to the letter L. There were a total of 24 pathways. The total time required to finish the test was calculated and the number of mistakes within the pathways were counted.

Statistical analysis

Data were analyzed with SPSS statistical software version 18.0 (Chicago, IL, USA). Categorical variables were expressed using percentages. Shapiro-Wilk normality test was used to test the distribution of numerical variables. Categorical variables were compared using chi-square test. For continuous variables, parametric Student’s t-test and non-parametric Mann-Whitney U test were used. Analysis of descriptive variables was presented as mean ± SD, while analysis of categorical variables was presented as percentile.

Statistical significance was set at p value <0.05.

Results

Twentyone patients (14 females and 7 males) took part in the study. Mean age was 43.57 years (±11.36), mean education period was 7.47 years (±3.48). Demographic variables of both groups are shown in Table 1.

Twelve patients (57%) had EEG abnormalities (focal or generalized slowing) while 9 patients (43%) had normal EEG and 13 patients (62%) had MRI abnormalities (nonspecific white matter lesions) while 8 patients (38%) had normal MRI. Six patients (29%) had both EEG abnormalities and MRI abnormalities.

Patients got mean 11.71 (±66.67) points from BDI while controls got 11.42 (±10.05) points, which showed no statistical significance (p=0.442) (Table 1).

Mean time taken for the Stroop test subgroups (ST1, ST2, ST3, ST4, ST5) were 17.76 (±17.11) seconds, 17.71 (±11.34) seconds, 19.61 (±8.69) seconds, 28.09 (±18.38) seconds, 41.19 (±21.22) seconds consecutively in patients while they were 13.76 (±4.83) seconds, 14.66 (±4.68) seconds, 19.14 (±8.64) seconds, 26.57 (±15.31) seconds and 39.04 (±28.85) seconds consecutively in the control group. Mean total time for all Stroop tests was 124.66 (±60.72) seconds in patients versus 114.14 (±53.53) seconds in the controls. Patients made mean 4.61 (±6.23) total mistakes while controls made mean 4.33 (±6.37) mistakes. Patients made mean 2.95 (±2.78) corrections while controls made mean 2.23 (±2.09) corrections. None of the results for ST showed significant difference between the two groups (p>0.05)

Mean CWAT and CFT scores of patients were as follows 17.85 (±5.40) and 23.23 (±9.69) in patients and 18.28 (±4.48) and 21.61 (±11.78) in the control group. Similarly perseveration scores in CWAT and CFT were; 0.90 (±1.13) in patients vs. 0.90 (±1.17) in controls and 1.04 (±1.80) in patients vs. 0.52 (±0.60) in controls. No significant difference was detected between the two groups (p>0.05).

Mean DF scores in patients were 5.09 (±0.94) and 4.85 (±1.01) in the controls while mean DB scores were 3.57 (±1.16) in patients and 2.95 (±1.59) in controls. Study groups showed no significant difference by means of DF and DB (p>0.05) (Table 4).

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**Table 1. Demographic variables of both study groups**

|                        | Group I (n=21) | Group II (n=21) | p   |
|------------------------|---------------|----------------|-----|
| Sex                    | 14 f (66.7%), 12 f (57.1%), 7 m (33.3%) | 9 m (42.9%) | 0.525 |
| Mean age (years)       | 43.57 (±11.36) | 44.04 (±11.61) | 0.894 |
| Educational level (years) | 7.47 (±3.48) | 7.71 (±3.14) | 0.730 |

Statistical significance: p<0.05.

Group I: sarcoidosis patients; Group II: healthy controls

f: female; m: male
Mean TMB time for patients was 159.19 (±85.96) seconds while it was 145.42 (+91.03) seconds in controls. Mean number of mistakes in TMB was 14.23 (±9.41) in patients and 14.80 (±10.51) in controls. Both domains showed no significant difference (p>0.05). All test scores for both study groups are shown in Table 2.

Comparison of Group IA (patients with EEG abnormalities) with Group IB (patients with normal EEG) and comparison of Group Ix (patients

| Table 2. All test results for both study groups |
|-----------------------------------------------|
| Group I (n:21) | Group II (n:21) | p |
| Mean BDI 11.7143 (±6.67190) | 11.4286 (±10.05272 ) | 0.442 |
| Mean ST1 (seconds) 17.7619 (±17.11696 ) | 13.7619 (±4.83637) | 0.356 |
| Mean ST2 (seconds) 17.7143 (±11.34523 ) | 14.6667 (±4.68330) | 0.405 |
| Mean ST3 (seconds) 19.6190 (±8.69756 ) | 19.1429 (±8.64457 ) | 0.940 |
| Mean ST4 (seconds) 28.0952 (±18.38724) | 26.5714 (±15.31852) | 0.970 |
| Mean ST5 (seconds) 41.1905 (±21.22644) | 39.0476 (±28.85737) | 0.513 |
| Mean STT (seconds) 124.6667 (±60.72506) | 114.1429 (±53.53997) | 0.678 |
| Mean #mistakes in ST 4.6190 (±6.23279) | 4.3333 (±6.37443 ) | 0.429 |
| Mean #corrections in ST 2.9524 (±2.78345) | 2.2381 (±2.09535 ) | 0.467 |
| Mean CWAT 17.8571 (±5.40635) | 18.2857 (±4.48490) | 0.640 |
| Mean #perseverations in CWAT 0.9048 (±1.13599) | 0.9048 (±1.17918) | 0.946 |
| Mean CFT 23.2381 (±9.69487) | 21.6190 (±11.78336) | 0.351 |
| Mean #perseverations in CFT 1.0476 (±1.80212) | 0.5238 (±0.60159) | 0.470 |
| Mean DF 5.0952 (±0.94365) | 4.8571 (±1.01419 ) | 0.436 |
| Mean DB 3.5714 (±1.16496 ) | 2.9524 (±1.59613 ) | 0.249 |
| Mean TMB time(seconds) 159.1905 (±85.96372) | 145.4286 (±91.03437 ) | 0.406 |
| Mean #mistakes in TMB 14.2381 (±9.41225) | 14.8095 (±10.51484) | 0.765 |

Statistical significance: p<0.05
Group I: sarcoidosis patients; Group II: healthy controls
BDI: Beck Depression Inventory; ST1: Stroop Test Domain 1; ST2: Stroop Test Domain 2; ST3: Stroop Test Domain 3; ST4: Stroop Test Domain 4; ST5: Stroop Test Domain 5; STT: Stroop Test Total; CWAT: Controlled Word Association Test; CFT: Category Fluency Test; DF: Digit Span Forward; DB: Digit Span Backwards; TMB: Trail Making Test B

| Table 3. Comparison of sarcoidosis patients with and without EEG abnormalities (Group IA vs. Group IB) |
|-----------------------------------------------|
| Group IA (n:12, 57%) | Group IB (n:9, 43%) | p |
| Mean BDI 11.7500 (±7.37471) | 11.6667 (±6.04152) | 0.978 |
| Mean ST1 (seconds) 13.7500 (±2.76751 ) | 23.1111 (±25.79944) | 0.602 |
| Mean ST2 (seconds) 15.5000 (±3.34392) | 20.6667 (±17.00735 ) | 0.862 |
| Mean ST3 (seconds) 18.6667 (±7.70281) | 20.8889 (±10.21573 ) | 0.917 |
| Mean ST4 (seconds) 28.0000 (±20.31569) | 28.2222 (±16.66417) | 0.651 |
| Mean ST5 (seconds) 44.2500(22.71613) | 37.1111 (±19.58975) | 0.345 |
| Mean STT (seconds) 120.1667 (±49.90688) | 130.6667 (±75.65216) | 0.554 |
| Mean #mistakes in ST 5.7500 (±7.91001) | 3.1111 (±2.57121) | 0.972 |
| Mean #corrections in ST 3.1667 (±1.89896) | 2.6667 (±3.77492) | 0.277 |
| Mean CWAT 17.9167 (±6.77507) | 17.7778 (±3.15348) | 0.602 |
| Mean #perseverations in CWAT 1.0000 (±1.20605 ) | 0.7778 (±1.09291) | 0.651 |
| Mean CFT 22.5000 (±11.50099) | 24.2222 (±7.15503 ) | 0.508 |
| Mean #perseverations in CFT 1.1667 (±2.20880 ) | 0.8889 (±1.16667) | 1.00 |
| Mean DF 4.1111 (±1.45297 ) | 4.9167 (±0.90034) | 0.382 |
| Mean DB 3.1667 (±0.71774) | 4.1111 (±4.52979) | 0.111 |
| Mean TMB time(seconds) 142.0833 (±63.96229 ) | 182.0000 (±108.74167) | 0.304 |
| Mean #mistakes in TMB 16.0833 (±10.28201) | 11.7778 (±8.01214) | 0.382 |

Statistical significance: p<0.05
Group IA: sarcoidosis patients with EEG pathologies; Group IB: sarcoidosis patients with normal EEG
BDI: Beck Depression Inventory; ST1: Stroop Test Domain 1; ST2: Stroop Test Domain 2; ST3: Stroop Test Domain 3; ST4: Stroop Test Domain 4; ST5: Stroop Test Domain 5; STT: Stroop Test Total; CWAT: Controlled Word Association Test; CFT: Category Fluency Test; DF: Digit Span Forward; DB: Digit Span Backwards; TMB: Trail Making Test B
with MRI abnormalities) with Group Iy (patients with normal MRI) showed no significant difference (p>0.05) and are shown in Tables 3 and 4. Similarly, comparison of Group Iα (disease duration less than 24 months) with Group Iβ (disease duration more than 24 months) showed no significance (p>0.05) (Table 5).

### Table 4. Comparison of sarcoidosis patients with and without MRI abnormalities (Group Ix vs. Group Iy)

|                  | Group Ix (n:8, 38%) | Group Iy (n:13, 62%) | p      |
|------------------|---------------------|-----------------------|--------|
| Mean BDI         | 10.8750 (±6.46833)  | 12.2308 (±7.00183)    | 0.663  |
| Mean ST1 (seconds) | 23.3750 (±27.44833) | 14.3077 (±3.85972)    | 0.374  |
| Mean ST2 (seconds) | 20.8750 (±17.60225) | 15.7692 (±4.79850)    | 0.750  |
| Mean ST3 (seconds) | 20.5000 (±10.60997) | 19.0769 (±7.71861)    | 0.547  |
| Mean ST4 (seconds) | 26.6250 (±12.63711) | 29.0000 (±21.63331)   | 0.750  |
| Mean ST5 (seconds) | 39.0000 (±16.49242) | 42.5385 (±24.23020)   | 0.916  |
| Mean STT (seconds) | 130.3750 (±71.19377)| 121.1538 (±56.16174)  | 0.804  |
| Mean #mistakes in ST | 4.3750 (±6.05930)   | 4.7692 (±6.55939)     | 0.595  |
| Mean #corrections in ST | 2.2500 (±1.83225)  | 3.3946 (±3.22848)     | 0.378  |
| Mean CWAT        | 16.2500 (±2.37547)  | 18.8462 (±5.30011)    | 0.297  |
| Mean #mistakes in CWAT | 1.2500 (±1.38873)  | 0.6923 (±0.94733)     | 0.374  |
| Mean CFT         | 20.1250 (±7.58641)  | 25.1538 (±10.61325)   | 0.259  |
| Mean #perseverations in CFT | 1.3750 (±2.72226)  | 0.8462 (±0.98710)     | 0.301  |
| Mean DF          | 5.0000 (±0.75593)   | 5.1538 (±1.06819)     | 0.804  |
| Mean DB          | 2.8750 (±1.83452)   | 4.0000 (±1.15470)     | 0.130  |
| Mean TMB time(seconds) | 151.7500 (±57.98707)| 163.7692 (±101.46523)| 0.804  |
| Mean #mistakes in TMB | 18.8750 (±8.99901) | 11.3846 (±8.78956)    | 0.121  |

Statistical significance: p<0.05

**Group Ix**: sarcoidosis patients with MRI pathologies; **Group Iy**: sarcoidosis patients with normal MRI

BDI: Beck Depression Inventory; ST1: Stroop Test Domain 1; ST2: Stroop Test Domain 2; ST3: Stroop Test Domain 3; ST4: Stroop Test Domain 4; ST5: Stroop Test Domain 5; STT: Stroop Test Total; CWAT: Controlled Word Association Test; CFT: Category Fluency Test; DF: Digit Span Forward; DB: Digit Span Backwards; TMB: Trail Making Test B

### Table 5. Comparison of sarcoidosis patients with disease duration less vs. more than 24 months (Group Iα vs. Group Iβ)

|                  | Group Iα (n:14) | Group Iβ (n:7) | p       |
|------------------|-----------------|----------------|---------|
| Mean BDI         | 10.5714 (±6.50106) | 14.0000 (±6.90411) | 0.278  |
| Mean ST1 (seconds) | 18.2857 (±21.04365) | 16.7143 (±3.90360) | 0.067  |
| Mean ST2 (seconds) | 17.7857 (±13.51454) | 17.5714 (±5.76938) | 0.360  |
| Mean ST3 (seconds) | 19.3571 (±8.58986)  | 20.1429 (±9.58173) | 0.585  |
| Mean ST4 (seconds) | 28.0000 (±21.11871) | 28.2857 (±12.67166)| 0.360  |
| Mean ST5 (seconds) | 37.1429 (±20.48586) | 49.2857 (±21.86103)| 0.197  |
| Mean STT (seconds) | 121.0000 (±67.29156)| 132.0000 (±48.85352)| 0.322  |
| Mean #mistakes in ST | 4.5000 (±3.82087)  | 4.8571 (±6.41427)  | 1.00   |
| Mean #corrections in ST | 2.7143 (±2.30146)  | 3.4286 (±3.73529)  | 0.592  |
| Mean CWAT        | 18.4286 (±6.32108) | 16.7143 (±6.92770) | 0.507  |
| Mean #perseverations in CWAT | 0.9286 (±1.14114)  | 0.8571 (±2.12499)  | 0.799  |
| Mean CFT         | 24.8571 (±10.33930)| 20.0000 (±7.95822) | 0.291  |
| Mean #perseverations in CFT | 1.2143 (±2.08211)  | 0.7143 (±1.11270)  | 0.636  |
| Mean DF          | 5.3571 (±0.92878)  | 4.5714 (±0.78680)   | 0.094  |
| Mean DB          | 3.6429 (±1.21574)  | 3.4286 (±1.13389)   | 0.689  |
| Mean TMB time(seconds) | 151.3571 (±76.89614) | 174.8571 (±106.73086)| 0.568  |
| Mean #mistakes in TMB | 13.9286 (±9.66727) | 14.8571 (±9.59911) | 0.743  |

Statistical significance: p<0.05

**Group Iα**: sarcoidosis patients with MRI pathologies; **Group Iβ**: sarcoidosis patients with normal MRI

BDI: Beck Depression Inventory; ST1: Stroop Test Domain 1; ST2: Stroop Test Domain 2; ST3: Stroop Test Domain 3; ST4: Stroop Test Domain 4; ST5: Stroop Test Domain 5; STT: Stroop Test Total; CWAT: Controlled Word Association Test; CFT: Category Fluency Test; DF: Digit Span Forward; DB: Digit Span Backwards; TMB: Trail Making Test B

### Discussion

This study showed that sarcoidosis patients without neurological involvement had no decline in executive functions when compared to healthy controls. Patients showed similar performance with healthy controls by means of neurocognitive tests.
Neurological disease in sarcoidosis is known to develop early in the course of sarcoidosis (24). Accordingly, we included patients who have not been treated by steroids or immunosuppressants yet. This approach served two goals; one of them was to perform the study with early stage patients without a documented neurological involvement, second one was to avoid the interfering effect of steroids and immunosuppressants which are the main therapeutics for NS on cognitive functions. Nevertheless, we compared the results of patients suffering from the disease for less and more than 24 months. We found no significant difference (p>0.0.5). Considering the mechanisms in neurosarcoidosis a thorough explanation is necessary to understand this outcome.

Anatomical lesions caused by sarcoidosis may play role in cognitive decline. Sarcoid lesions have been found in almost every part of the CNS while sarcoid granulomas have affinity for cerebral vessels (25, 26). Hence, areas of cerebral ischaemia and infarction due to granulomatous angiitis of the cerebral vessels which cause the most common radiological findings as nonspecific white matter lesions have also been described (25). Granulomatous infiltration of the cerebral vessels, perivascular granulomatous inflammation or psychological stress have been blamed to be associated with neuropsychiatric conditions like depression or encephalopathy in neurosarcoidosis, formerly. Thirty-eight percent of our patients had nonspecific WML. However, our patients with MRI lesions had no significant difference than patients with normal MRI by means of executive functional decline (p>0.0.5). Similarly, EEG slowings have been shown to be a marker for cognitive impairment especially in attention and executive functions (27). Finnigan and Robertson have linked EEG/alpha slowing to substantial cognitive decline in healthy older adults (28). A recent study by our group has demonstrated that 46.7% of sarcoidosis patients without neurological involvement showed intermittent EEG slowings (29). This significant finding inspired us to further investigate the cognitive status of sarcoidosis patients. However, patients with EEG slowings showed no different results than patients with normal EEG. EEG or MRI abnormalities in our patients had no effect on impairment of executive functions. This was a controversial finding which may be related to relatively small sample size. But detecting similar results in patients with and without EEG or MRI abnormalities in sarcoidosis patients preoccupied us a different mechanism which can not be detected via EEG or MRI in the occurrence of cognitive decline in neurosarcoidosis. One of the latest approaches to understand the nature of cognitive impairment is the inflammation theory. Ongoing inflammatory disease has been released to be the cause of cognitive decline in several case reports (30).

Similarly, TNF-alpha and IL-2 which are released by macrophages in NS have been shown to cause long-term cognitive decline (31-33). Selective accumulation of TNF-alpha and sIL-2R in basal ganglia and prefrontal structures have already been dictated (10-12). Considering the inflammatory basis of sarcoidosis, it is hard to exclude cognitive decline only depending on the conventional neuropsychological assessment and obviously additional tests are required. Rather than a few case reports mentioning cognitive impairment in neurosarcoidosis, no further investigations were available until Beste et al. clearly demonstrated that NS was not related with nonspecific changes in cognitive control while specific alterations in cognition like processes in action ordering which were highly dependent on immunological changes showed deficits in NS patients (7). However, a major limitation of this study according to us was that the actual medications of the NS patients which are usually composed of steroids and/or immunosuppressants both of which are known to affect cognition have not been remarked. Before concluding on a general judgement on neurological assessment, we wanted to exclusively evaluate executive functions in addition to Beste et al. and we improved our study by excluding the interfering effect of medications depending on our patient selection.

While steroids are known to negatively effect cognition, immunosuppressants have controversial effects on cognition (34-37).

Certain individuals have been reported to develop “steroid dementia syndrome” after glucocorticoid treatment (38). Also, chronic exposure to glucocorticoids may detoriate hippocampal function (39-41) and even may cause a reduce in hippocampal volume (38). A previous study by Brown et al. reported smaller hippocampal volumes and memory deficits in patients treated chronically with a mean dose of 15.6 mg of predisone for a mean duration of 92 months compared with control patients (41). Normal therapeutic procedure for sarcoidosis is us-
ally shorter (9-12 months) in time but remarkably higher in dosage which starts with 40 mg of prednisone daily even though tapered monthly (2).

We conclude that conventionally detectable executive functions are not impaired in sarcoidosis in the absence of neurological involvement despite the inflammatory nature of the disease. This result may be commented in two ways: first of them is that pure neurological assessment tests are not competent in detecting impairment of executive functions in NS. Secondly, regarding the limited data on cognitive functions in NS, cognitive decline in NS may be related to the steroid and/or immunosuppressant treatment in neurologically involved patients. For this reason clinicians should meticulously evaluate patients before deciding a long term treatment in NS. A thorough neurocognitive assessment accompanied by additional electrophysiological or radiological testing which include detailed paradigms might be planned for patients before and periodically after the initiation of therapy. Some of the immunosuppressive agents may be a choice for steroid sparing in order to initiate of therapy. Some of the immunosuppressive agents may be a choice for steroid sparing in order to protect cognition in NS (42-45) while some of them should be avoided (36, 37).

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