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# Evidence of dysexecutive syndrome in patients with acromegaly

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**Abstract**

*Purpose* This study aimed to explore different aspects of executive function in patients with acromegaly and investigate the cause of dysexecutive syndrome in these patients.

*Methods* We conducted five typical executive function tests (Stroop test, verbal fluency [VF] test, Hayling Sentence Completion Test [HSCT], N-back test, and Sustained Attention to Response Task [SART]) on 42 acromegalic patients and 42 strictly matched healthy controls. Comparative analyses were conducted for five major executive function domains. The Dysexecutive Questionnaire (DEX) was used to assess patients' subjective feelings about their executive function. All patients underwent a magnetic resonance imaging (MRI) examination and a blood test to determine their pituitary hormone levels before the tests were performed.

*Results* The patients exhibited worse results on the Stroop test, VF test, HSCT and N-back test compared to the healthy control group. Moreover, part B of the HSCT and the N-back test performance were negatively correlated with IGF-1 concentrations, and the duration of the disease was significantly associated with the Stroop color task results.

*Conclusions* Acromegalic patients were severely impaired in semantic inhibition, executive processing, working memory and executive inhibition, and they have realized a portion of these deficits. A high level of IGF-1, disease duration may contribute to the impairment of specific aspects of executive function.

**Keywords** Acromegaly · Dysexecutive function · IGF-1 · Disease duration

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## Introduction

Acromegaly is a rare chronic disease, and in 99% of cases, it is caused by a growth hormone (GH)-secreting pituitary adenoma. The aberrant secretion of GH also leads to excessive secretion of insulin-like growth factor-1 (IGF-1), which is responsible for the major symptoms of acromegaly. This disease is typically diagnosed with an average delay of 5–10 years after patients have undergone an insidiously long clinical course [1, 2]. The initial symptom is typically enlargement of the hands and feet. Enlargement of the supraorbital ridges, tongue, nose and lips may also occur. However, metabolic complications, such as an impaired glucose tolerance, diabetes, an abnormal lipid profile and hypertension are much more serious consequences of the disease that can lead to a higher incidence of ischemic heart disease and heart failure. Cardiovascular events are the main cause of mortality in patients with acromegaly [3–5].

Acromegalic patients have been observed to have comprehensive cognitive dysfunctions, especially in memory and executive function. Leon-Carrion et al. assessed the cognitive function of 16 patients diagnosed with acromegaly and 16 healthy control subjects [6]. The researchers examined major cognitive domains including attention, executive functioning, short- and long-term memory (verbal and visual), visuoconstructive ability, and language skills (verbal fluency) [6]. They found that short- and long-term memory were most severely impaired, and memory performance was negatively correlated with GH and IGF-1 concentrations [6]. Executive function is the major component of cognitive processes, including inhibition, working memory, reasoning, task flexibility, problem solving, planning, and execution [7–9]. The different types of executive functions in patients with acromegaly remain unclear. Furthermore, the mechanisms of the dysexecutive function of those patients are also unknown. Our study aimed to determine whether acromegalic patients and who were exposed to high levels of IGF-1 for an extended time had different aspects of executive function that were impaired and to investigate the cause of dysexecutive syndrome in these patients.

## Methods

### Study participants

Based on the inclusion and exclusion criteria, we enrolled 42 acromegaly subjects in our study. The patients were admitted to Beijing Tiantan Hospital at Capital Medical University in China from February 1, 2016 to December 1, 2016. The inclusion criteria were as follows: (1) age between 18 and 55 years; (2) a confirmed GH-secreting adenoma that was not treated with surgery or radiation therapy; (3) no other brain diseases, such as cerebrovascular disease; and (4) no local neurological dysfunction such as vision loss and dyskinesia that would prevent the completion of the tests. The diagnosis of acromegaly was based on an IGF-1 concentration above the normal limit adjusted for age and sex [10]. Surgical pathology was also used to confirm the tumor as GH-secreting PA after surgical tumor excision. The exclusion criteria were as follows: (1) IQ < 70; (2) diagnosis of a family history of mental diseases, mania and other mental illness; (3) serious systemic disease, such as cardiac disease; and (4) patients who did not complete all tests.

We recruited 42 right-handed healthy volunteers as a control group; these volunteers were strictly matched to the patients according to their general conditions. Most of the volunteers were the patients' family members. Table 1 shows the patient demographic and clinical information.

### Clinical data

Magnetic resonance imaging (MRI) and a blood test to determine the level of pituitary hormones were performed during the diagnostic hospitalization. The scoring methods of both Knosp et al. [11] and Cottier et al. [12] were used to evaluate the tumor invasion on MRI. Invasive features were noted as follows. The tumor crossed the lateral line (LL) of the intracavernous and supracavernous portions of the internal carotid artery (ICA) or the percentage of intracavernous ICA encasement was > 67%. The size of the adenoma was measured as the largest reported dimension on MRI.

**Table 1** Sociodemographic and clinical characteristic: acromegaly patients and healthy controls

| Variable | Patients | Controls | t-test/Chi square test | p value |
|---|---|---|---|---|
| No. of cases | 42 | 42 | | |
| Mean age ± SD | 41.429 ± 9.833 | 38.048 ± 8.319 | 2.894 | 0.093 |
| Sex | | | 0.194 | 0.659 |
|   Male | 25 | 23 | | |
|   Female | 17 | 19 | | |
| Social status | | | 0.057 | 0.811 |
|   City | 13 | 12 | | |
|   County village | 29 | 30 | | |
| Mean years of education ± SD | 10.86 ± 2.710 | 11.83 ± 2.668 | 2.767 | 0.100 |
| Mean estimated IQ ± SD | 98.024 ± 10.004 | 101.5 ± 8.657 | 2.869 | 0.094 |
| Invasive adenoma | 12 | | | |
| Non-invasive adenoma | 30 | | | |
| Mean duration of disease ± SD (years) | 5.603 ± 4.979 | | | |

## Neuropsychological tests

### IQ test

The Wechsler Adult Intelligence Scale-Third Edition (Chinese version) was used to evaluate the general intelligence of participants. The following four aspects were evaluated: Information, Digital Span, Similarity, and Arithmetic.

### Executive function tests

Both groups underwent a comprehensive executive function assessment of major executive domains, including executive processing, executive inhibition, semantic inhibition, sustained attention, and working memory.

Executive inhibition function can reduce the impact of irrelevant information and helps to respond appropriately to task-related information. It enables individuals to choose how they react and behave to adapt a changing environment rather than being unthinking creatures of habit. It can be assessed by the Stroop test [13]. In the Stroop task, participants were asked to name colors in three presentation formats, including dots, words, and colors. Both the dots and words have no correlation with the naming colors in the Stroop Dot and Stroop Word test. However, in the Stroop color test, participants are asked to name the colors of a set of words that spell the names of other colors. Due to the long-term reading experience, people owned a strong tendency to read words and have a lower response speed under the conditions of the color are inconsistent with meaning of the word. This phenomenon appears more obvious in people who impaired their executive inhibition function.

The Hayling Sentence Completion test (HSCT) is used to assess semantic initiation and semantic inhibition function [14]. This test consists of two parts, A and B, each containing 15 different sentences with the final word omitted. In the first section, the examiner reads each sentence aloud and the participant has to complete the sentences simply, yielding a simple measure of semantic initiation speed. The second part of the Hayling requires participants to complete a sentence with a nonsense ending word (and inhibition a sensible one), giving measures of inhibition ability and thinking time. The correct number, mean correct reaction time (RT) (RTs for total correct terms/correct number) and total time (sum of RTs for all terms) were collected. A shorter latency period and fewer errors on part A or part B indicated good semantic initiation or inhibition function [15].

We used the verbal fluency (VF) test to evaluate executive processing. VF test consist of verbalizing as many words as possible in one minute that either start with a specific letter of the alphabet or belong to a specific semantic category (animal names in the present study)

[16]. The total number and number of repetitions of animal names were used to measure the common performance in executive processing.

The working memory function was assessed by the N-back test [17]. Working memory refers to the system that is responsible for temporarily storing and processing information during the performance of complex cognitive tasks such as learning, memory, thinking and problem solving. In the N-back test, the participants were presented with a square and a plus sign ("+") on the test computer screen, and the relative locations of the images were unfixed. Participants were asked to finish 0-back, 1-back, and 2-back tasks in the current study. They were required to determine the various relative locations of the two figures in the 0-back task. The subjects were asked to keep the initial relative locations of the square and "+" in mind and to compare the location of the next presented figure. The 2-back task was the most difficult among the tests. For this task, participants were required to compare the relative locations of the square and "+" between the current trial and the trial before the last. The accuracy and mean RT of each task were recorded by the computer software [15].

The sustained attention to response task (SART) is used to investigate the sustained attention function [18, 19]. Sustained attention is a fundamental executive function. Individuals with impaired sustained attention function have difficulty focusing on targets and tasks and display 'absent-minded' lapses of action. The participants were presented 225 single digits over 4.3 min in the computerized test. Each digit was presented for 250 msec, followed by a 900-msec mask. The subjects were required to click the left mouse button in response to the digits except on 25 occasions, when the digit "3" would randomly appear. The results were recorded as follows: hits (the accuracy with which the participant pressed the mouse when a number other than 3 appeared), the hit RT (the mean RT of the hit), and correct rejections (the accuracy with which the participant did not press the mouse when the number 3 appeared) [15]. Correct rejections reflect the efficiency of endogenous resistance to the inattentive, 'absentminded' response.

### Dysexecutive questionnaire

The Dysexecutive Questionnaire (DEX) contains a total of 20 items that were administered to assess the participants' subjective feelings about their executive functioning. Five executive function factors were derived as follows: inhibition (factor 1), intentionality (factor 2), knowing-doing dissociation (factor 3), in-resistance (factor 4), and social regulation (factor 5). This test was administered to participants aged 18–50 years [20].

## Testing procedure

All participants were evaluated by the above tests after signing an informed consent form. The tests were conducted in fixed locations with the same sequence. We expressed our appreciation to all participants for their involvement in the study. The tests were approved by the Institutional Review Board of Beijing Tiantan Hospital in affiliation with Capital Medical University.

## Statistical analysis

A one-way ANOVA was conducted to evaluate performance differences between acromegaly patients and healthy subjects. Correlation analysis was also performed to assess the correlations of hormone concentration, tumor size and time interval from presentation to assessment with all of the test items. The level of statistical significance was set at 0.05.

## Results

### Comparison between acromegaly patients and healthy controls

Acromegaly patients exhibited poorer performance than the healthy controls on most tests. Table 2 summarizes the executive function results for both groups. Both the total time and error number from the Stroop color test were significantly different for acromegaly patients and healthy controls ($F = 16.074$, $p < 0.05$, total time; $F = 30.020$, $p < 0.05$, error number), indicating that compared to the healthy controls, the patients had poorer executive inhibition functionality. The total score on the VF test was significantly lower for acromegaly patients than that for healthy controls ($F = 17.165$, $p < 0.05$), indicating that the patients had poorer executive processing than the healthy controls. The total time and mean correct RT ($F = 13.714$, $p = 0.001$, for total time; $F = 13.714$, $p = 0.001$, for mean correct RT) for part B, and the number of type A errors on part B of the HSCT ($F = 10.152$, $p = 0.002$) were significantly different between the patients with acromegaly and healthy controls, suggesting that the semantic inhibition function may became impaired in acromegaly patients. Although the accuracy score of the 0-back task ($F = 2.604$, $p = 0.111$) did not show a significant difference between the two groups, the patients' performance on the 1-back and 2-back tasks of the N-back test ($F = 7.246$, $p = 0.009$ and $F = 15.377$, $p < 0.05$) was poorer than that of the healthy group, indicating that the working memory of acromegaly patients was significantly poorer than that of the healthy controls. However, the patients' performance for the hit time, hit RT and correct rejections of the SART test did not result in any significant

difference with the healthy group. We also found that factor 2 and factor 5 of the DEX were significantly different between the patients group and the healthy group ($F = 5.656$, $p = 0.020$; $F = 7.017$, $p = 0.010$), indicating that patients with acromegaly are aware of their dysexecutive syndrome with regarded to intentionality and social regulation factors.

### Correlations among IGF-1, duration of disease, tumor size and executive function

The relationships between executive dysfunctions and IGF-1 levels are summarized in Table 3. We found that a high IGF-1 level contributed to the impairment of semantic inhibition and working memory function in patients with acromegaly. The IGF-1 levels of acromegaly patients were significantly and positively correlated with the total time and mean correct RT on part B of the HSCT ($r = 0.384$, $p = 0.021$; $r = 0.406$, $p = 0.014$) and with the RT of the 0-back and 1-back tasks ($r = 0.329$, $p = 0.041$; $r = 0.516$, $p = 0.001$), indicating that higher IGF-1 levels were associated with these poorer task performances. No significant correlations were detected among IGF-1 levels and the Stroop, SART and DEX tests. We also found that the time interval from the onset of patients' complaints until assessment was significantly associated with the total time and error number on the Stroop color task ($r = 0.352$, $p = 0.022$; $r = -0.485$, $p = 0.001$). No correlations were found between the tumor size and test results.

## Discussion

Our study indicated that acromegaly patients presented impairments in executive function; this result is also supported by the published literature [21, 22]. Additionally, different aspects of executive functions, such as semantic inhibition, executive processing, and working memory, were found to be impaired in acromegaly patients. During our testing process, both the patients and the healthy group finished the Stroop dot test with no differences, but an obvious difference was found in the Stroop color test, indicating that acromegaly patients presented much poorer executive inhibition as the task difficulty increased. Moreover, compared to patients with acromegaly, we found that the healthy controls always applied a strategy to finish the test; they employed a classified description and summary to increase the total number of the VF test. However, few patients with acromegaly can use such methods. Thus, the patients may exhibit poorer executive functioning and task flexibility. According to the results of the N-back test, acromegaly patients had difficulty in working memory tasks. Leon-Carrion et al. [6, 23, 24] also found that the impairment of working memory in acromegaly patients was associated with frontal lobe

**Table 2** Performances of acromegaly patients and controls on executive function tests

| Test | Patients* | Controls* | F value | p value |
|---|---|---|---|---|
| Stroop | | | | |
|   Dot condition | | | | |
|     Total time | 14.379 ± 2.471 | 13.396 ± 2.391 | 3.431 | 0.068 |
|     No. of errors | 0.14 ± 0.417 | 0.05 ± 0.216 | 1.726 | 0.193 |
|   Word condition | | | | |
|     Total time | 19.329 ± 3.912 | 15.941 ± 3.092 | 19.400 | <0.001[a] |
|     No. of errors | 0.76 ± 0.958 | 0.21 ± 0.520 | 10.606 | 0.002[a] |
|   Color condition | | | | |
|     Total time | 32.096 ± 9.814 | 25.368 ± 4.686 | 16.074 | <0.001[a] |
|     No. of errors | 2.71 ± 1.330 | 1.05 ± 1.530 | 30.020 | <0.001[a] |
| VF test | | | | |
|   Total no. | 17.67 ± 3.490 | 21.07 ± 3.990 | 17.165 | <0.001[a] |
|   Repeat no. | 1.24 ± 1.031 | 1.100 ± 0.944 | 0.419 | 0.519 |
| HSCT | | | | |
|   Part A | | | | |
|     Total time | 26.759 ± 9.443 | 24.096 ± 5.395 | 2.455 | 0.121 |
|     No. correct | 14.632 ± 0.541 | 14.691 ± 0.604 | 0.209 | 0.649 |
|     Mean correct RT | 1.769 ± 0.602 | 1.562 ± 0.362 | 3.532 | 0.064 |
|   Part B | | | | |
|     Total time | 90.257 ± 41.308 | 60.718 ± 29.960 | 13.714 | 0.001[a] |
|     No. correct | 5.615 ± 3.345 | 7.714 ± 3.782 | 6.956 | 0.001[a] |
|     No. Type A error | 4.308 ± 2.811 | 2.524 ± 2.211 | 10.152 | 0.002[a] |
|     No. Type B error | 5.101 ± 2.197 | 4.762 ± 2.526 | 0.302 | 0.584 |
|     Mean correct RT | 6.674 ± 4.088 | 4.097 ± 1.983 | 13.314 | 0.001[a] |
| Nack test | | | | |
|   0-back | | | | |
|     RT (msec) | 568.665 ± 115.489 | 490.087 ± 91.524 | 11.766 | 0.001[a] |
|     Accuracy | 0.967 ± 0.033 | 0.980 ± 0.039 | 2.604 | 0.111 |
|   1-back | | | | |
|     RT (msec) | 840.326 ± 198.635 | 751.117 ± 134.129 | 5.722 | 0.019[a] |
|     Accuracy | 0.663 ± 0.178 | 0.754 ± 0.127 | 7.246 | 0.009[a] |
|   2-back | | | | |
|     RT (msec) | 970.498 ± 192.932 | 889.788 ± 239.409 | 2.695 | 0.105 |
|     Accuracy | 0.384 ± 0.164 | 0.526 ± 0.160 | 15.377 | <0.001[a] |
| SART | | | | |
|   Hit | 0.964 ± 0.041 | 0.977 ± 0.029 | 2.990 | 0.088 |
|   Hit RT (msec) | 421.524 ± 54.94 | 398.05 ± 79.654 | 2.433 | 0.123 |
|   Correct rejections | 0.857 ± 0.157 | 0.881 ± 0.137 | 0.569 | 0.453 |

*Data given as mean ± SD

[a] Statistically significant

function. Consistent with previous studies [6, 23, 24], the working memory test performance was negatively correlated with the excess concentration of IGF-1. The human hippocampus and its widespread connections with the neocortex are essential components of memory function. Physiological IGF-1 levels maintain cognitive function in the adult brain. However, prolonged overexposure to IGF-1 can result in brain-insulin resistance, promoting tau hyperphosphorylation and amyloid accumulation and leading to synaptic loss. These neurophysiological or neuroanatomical changes injure the brain areas with more binding sites to somatotropic axis hormones and contribute to the cognitive dysfunction in active acromegaly [6, 25]. In addition to the N-back task, the HSCT test results were also negatively correlated with the IGF-1 level, indicating that in acromegaly patients, exposure to high levels of IGF-1 may contribute to the impairment of semantic inhibition function.

**Table 3** Correlations between IGF1 levels and executive dysfunctions

| Executive function | IGF1 level |
|---|---|
| Part B of HSCT | NS* |
| Total time | r = 0.384, p = 0.021 |
| No. correct | NS* |
| No. Type A error | NS* |
| No. Type B error | NS* |
| Mean correct RT | r = 0.406, p = 0.014 |
| N-back test | NS* |
| 0-back RT (msec) | r = 0.329, p = 0.041 |
| 0-back Accuracy | NS* |
| 1-back RT (msec) | r = 0.516, p = 0.001 |
| 1-back Accuracy | NS* |
| 2-back RT (msec) | NS* |
| 2-back Accuracy | NS* |

*NS* means no significance

$p < 0.05$ was considered a significant difference

The dysexecutive syndrome was also reflected by the results of factor 2 and factor 5 of the DEX, indicating that patients with acromegaly also recognized their dysexecutive condition with regard to intentionality and social regulation [20]. Moreover, our study also showed that the impairments of executive inhibition and working memory function in acromegaly patients were significantly associated with the time interval between presentation and assessment. Patients with acromegaly show less activation in brain areas strongly associated with cognitive function, i.e., the prefrontal and middle temporal cortices [6]. Neuropsychological evidence suggests that executive processing is intimately connected with the intact function of the prefrontal cortices [8]. However, this brain area shows considerable age-related neuronal loss and decline in white matter integrity [26]. Furthermore, a growing body of evidence suggests that the GH/IGF-1 axis that declines in parallel with cognitive function during aging is involved in neuroprotection, regeneration, and functional plasticity in the adult brain [27, 28]. Consistent with previous studies, our study indicated that the prolonged duration of symptoms may contribute to the impairment of executive function, particularly executive inhibition and working memory function. However, no association was found between the tumor size and executive function test performance, suggesting that tumor size may be not the impairment factor of the executive function in acromegaly patients.

We must acknowledge that this study has many limitations. First, the acromegaly patients in our study were recruited from a single center; therefore, the sample representation may not be optimal. Second, further neuroimaging should be performed to detect the association between the hypothalamo-pituitary-adrenal axis and the frontal lobe to explore the mechanisms of dysexecutive syndrome. Third, the invasive subgroup sample size was not sufficiently large to properly match many possible confounding factors of the noninvasive subgroup, especially the IGF-1 level; thus, we could not precisely detect the relationship between tumor invasion and executive dysfunctions.

Our findings suggest that the specific aspects of dysexecutive syndrome may exist in acromegaly patients, and a prolonged high level of IGF-1 and longer duration of disease may contribute to those impairments. In the future, our studies may focus on the mechanisms of executive function impairments and the executive condition after the tumor is removed by different neurosurgery methodologies.

## Conclusions

Our study revealed that acromegaly patients exhibited impairment in specific executive function domains, i.e., semantic inhibition, executive processing, working memory and executive inhibition. Patients were also partially aware of the dysexecutive syndrome in their daily lives. Our findings suggest that increased IGF-1 level, disease duration may contribute to the impairments of specific executive functions.

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