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FULL PAPER

Microstructural brain changes in acromegaly: quantitative analysis by diffusion tensor imaging

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Objective: We examined brain diffusion changes of patients with acromegaly. We searched whether there are differences in apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values between remission and non-remission patients with acromegaly and investigated any effect of time of hormone exposure on diffusion metrics.
Methods: The values of FA and ADC were calculated in a total of 35 patients with acromegaly and 28 control subjects. Patients were subdivided into remission and non-remission groups. We looked at brain FA and ADC differences among the groups and looked for any relation between the diffusion changes and time of hormone exposure among the patients with acromegaly.
Results: We found decreased FA and increased ADC values in some of the growth hormone responsive areas. There were no significant brain diffusion changes between remission and non-remission groups. The most affected areas were the hypothalamus, parietal white matter and pre-motor cortex in patients with acromegaly. In terms of hormone exposure time among the patients with acromegaly, there was no effect of disease duration on brain microstructural changes.
Conclusion: All patients with acromegaly showed increased brain diffusion with no relation to disease duration and treatment status. We suggested that in patients with acromegaly, brain damage had already occurred in the subclinical period before symptom onset.
Advances in knowledge: This study contributes to the understanding of the mechanisms in acromegaly.

Acromegaly is a rare chronic disease characterized by the overexpression of the growth hormone (GH), which leads to an increased production of insulin-like growth factor-1 (IGF-1). The estimated prevalence of the disease is 40 cases/10 million per year.[1] When there is a clinical suspicion of the disease, biochemical confirmation is required to establish the diagnosis.[2] The increase in morbidity and mortality associated with acromegaly is the result of excessive secretion of GH and IGF-1.[1] The earliest manifestations of acromegaly are most commonly hands, feet and/or facial changes.[3] However, usually patients are often diagnosed late at about 8 years after the onset of the disease.[4] Following treatment, if there is resolution of clinical symptoms and normalization of biochemical values, patients are defined as acromegaly in remission.

The central nervous system (CNS) is affected by long-term exposure to high levels of GH and IGF-1. These hormones affect the regulation of brain function, nerve cell growth and cognitive capabilities.[5] In the literature, there is a limited study about structural and metabolic changes in the brains of patients with acromegaly.[5–9] Diffusion-weighted imaging and diffusion tensor imaging (DTI) techniques provide microstructural information about biological tissue damage that cannot be obtained with other imaging modalities.[10] DTI has already improved the scientific understanding of many neurologic and psychiatric disorders.[10] It allows a non-invasive characterization of microstructural damage, and diffusion changes may be altered in response to underlying pathological changes in some conditions. To our knowledge, quantitative analysis of structural changes of the brain, such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values, by using DTI in patients with acromegaly has not been reported in the literature.

We investigated diffusion changes of the brain in patients with acromegaly by measuring ADC and FA values in different brain regions and compared them with those of a healthy control group. We also looked at whether there

are differences in ADC and FA values between remission and non-remission patients with acromegaly and looked for any effect of time of hormone exposure on diffusion metrics.

In this study, we present a feasible examination of the brain in patients with acromegaly using DTI technique. We tested the hypothesis that the possible changes in specific regions of the brain can be detected with DTI in acromegaly.

METHODS AND MATERIALS

A total of 35 patients (21 females and 14 males; mean age, 43 ± 12 years), previously diagnosed with acromegaly based on standard clinical criteria, were included in the study. All patients with acromegaly ($n = 35$) were accepted as Group 1. If these patients with acromegaly had resolved clinical symptoms and treatment-induced normal hormone profile, such as circulating IGF-1 reduced to age- and sex-adjusted normal ranges and GH during oral glucose tolerance test $<0.4\ \mu g\,l^{-1}$ or random GH $<1\ \mu g\,l^{-1}$,[11] they were called biochemically controlled patients with acromegaly or patients with acromegaly in remission (Group 2, $n = 16$; mean age, 41 ± 8 years). The rest were accepted as patients with acromegaly in non-remission (Group 3, $n = 19$; mean age, 45 ± 14 years). 28 healthy subjects (mean age, 42 ± 14 years) were taken as a control group. Another parameter, which was called "time of hormonal excess" was taken into consideration for all patients with acromegaly. We accepted the subclinical period as 8 years for all patients with acromegaly.[4] According to the literature, the time of hormonal excess was calculated by adding 8 years to the time period after the diagnosis.[4] Recruited control subjects revealed no history of clinical, neurological or psychiatric conditions in the context of an unrelated structural imaging study and no history or clinical symptoms of acromegaly. Exclusion criteria were territorial brain infarction, neoplasm and gross developmental anomaly. The procedures used were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The study protocol was approved by the institutional ethical committee (Bezmialem Vakif University School of Medicine, Istanbul, Turkey). All subjects were fully informed and gave their written informed consent.

Imaging technique

MRI was performed using 1.5-T system (MAGNETOM® Avanto; Siemens Medical Solutions, Erlangen, Germany). The MRI protocol consisted of an axial three-dimensional (3D) T_1 weighted scan with magnetization prepared rapid gradient echo [repetition time (TR)/echo time (TE)/TI = 2300/3/950 ms], an axial fluid attenuated inversion recovery scan image (TR/TE/TI = 8000/90/1900 ms), an axial T_2 weighted scan (TR/TE = 4530/100 ms), an axial single-shot, spin-echo planar imaging DTI scan (TR/TE = 6000/88 ms); field of view, 23 cm^2; 128 × 128 matrix and 32 contiguous slices each 3 mm thick throughout the brain using 2 excitations. 30 different diffusion orientation directions were used with $b = 1000\ s\,mm^{-2}$, and another image with no diffusion gradient was obtained ($b = 0\ s\,mm^{-2}$). The entire brain was imaged. A high-resolution whole-brain T_1 image, with the same slice thickness, was used to register the tensor data to structural volumes. The ADC and FA maps were reconstructed with the commercially available software, Leonardo workstation (Leonardo, Siemens, Erlangen, Germany). We tried to minimize partial volume effects and avoided averaging with cerebrospinal fluid (CSF) by inspecting the slices above and below the region and using smaller regions of interest (ROIs) in work areas. The FA was calculated in native space from the $b = 0\ s\,mm^{-2}$ image and 30 diffusion-weighted images ($b = 1000\ s\,mm^{-2}$).

Region of interest

In the patient groups, 18 distinct anatomical locations, which were previously investigated and shown to be related to GH and IGF-1 receptors or/and affected by GH and IGF-1 were selected for the analysis.[8,12–15] Although some regions have been previously studied in the literature, we could not measure these areas appropriately. FA values >0.20 were taken into account in our study as in the study of Zhang et al[16] because we wanted to avoid inclusion of surrounding grey matter or CSF tissues. Furthermore, data quality was reviewed and ROIs that contained visual misregistration or white matter (WM) hyperintensities were excluded. FA values were measured from the WM. The ROI was drawn using the T_1 weighted imaging then automatically transferred to the ADC and FA maps, which generated the values for each of the regions. We minimized partial volume effects by inspecting the slices above and below the region to avoid averaging with CSF. The radiologists carefully evaluated the selected regions in all patients by using a similar sized ROI. The mean ADC and FA values of measurements performed by two radiologists from the same areas were taken under consideration.

Statistically analysis

All statistical analyses were performed using a commercially available SPSS® release v. 17.0 software package (SPSS Inc., Chicago, IL). The results were presented as the mean ± standard deviation and percentages. To test quantitative differences between two groups displaying a normal distribution, *t*-test for independent variables was used. The differences among the three groups were compared using one-way analysis of variance, following which *post hoc* Tukey tests were used for comparisons between the two groups. For correlation analysis between the category variables, Pearson's correlation (correlation coefficient) was used and the distribution of category variables was tested by the Pearson's χ^2 test. A *p*-value <0.05 was considered statistically significant in all.

RESULTS

There was no significant age and gender difference between patients with acromegaly and the control group.

Mean ADC and FA values of each group in different brain regions are presented in Tables 1 and 2. Among the patients, 54.3% were in non-remission and 45.7% were in remission.

The FA values in the hypothalamus ($p < 0.001$) and parietal white matter ($p = 0.002$) decreased in Group 1 compared with those in the control group. The FA values in the hypothalamus ($p = 0.001$) decreased in Group 2 compared with those in the control group. The FA value in the hypothalamus ($p = 0.009$) decreased in Group 3 compared with those in the control group.

The ADC value in the pre-motor cortex ($p = 0.001$) increased in Group 1 compared with those in the control group. The ADC

Table 1. Mean apparent diffusion coefficient (ADC) values ($\times 10^{-6}$ mm^2 s^{-1}) of different brain regions in patients with acromegaly and the control group

Locations	ADC			
	Control ($n = 28$)	Non-remission ($n = 19$)	Remission ($n = 16$)	Total patients ($n = 35$)
Cerebellar cortex	743.32 ± 38	750.89 ± 38	772.63 ± 45	760.83 ± 42
Parahippocampal gyrus	798.50 ± 57	813.63 ± 54	810.94 ± 49	812.40 ± 51
Hippocampus	846.57 ± 41	866.79 ± 57	847.75 ± 65	858.09 ± 61
Amygdala	807.75 ± 44	784.58 ± 45	814.63 ± 43	798.31 ± 46
Hypothalamus	745.96 ± 49	738.26 ± 46	749.69 ± 40	743.49 ± 43
Middle temporal cortex	770.86 ± 52	786.00 ± 49	808.63 ± 57	796.34 ± 53
Thalamus	787.61 ± 37	768.84 ± 32	753.25 ± 36	761.71 ± 34
Orbitofrontal cortex	791.21 ± 47	802.05 ± 50	810.44 ± 53	805.89 ± 51
Caudate nucleus	761.71 ± 39	743.26 ± 40	741.13 ± 41	742.29 ± 40
Putamen	757.43 ± 33	739.95 ± 47	743.06 ± 26	741.37 ± 38
Genu of corpus callosum	799.07 ± 52	815.95 ± 46	796.38 ± 79	807.00 ± 63
Splenium of corpus callosum	754.43 ± 36	769.89 ± 72	761.38 ± 58	766.00 ± 65
Frontal white matter	777.57 ± 40	774.42 ± 45	772.13 ± 51	773.37 ± 47
Parietal white matter	745.86 ± 40	750.42 ± 34	771.25 ± 52	759.94 ± 44
Pre-motor cortex	740.39 ± 34[a,b]	755.00 ± 43	778.50 ± 48	765.74 ± 46
Dorsomedial frontal cortex	770.32 ± 41	787.11 ± 54	781.25 ± 41	784.43 ± 48
Dorsolateral frontal cortex	778.07 ± 35	788.58 ± 41	792.56 ± 49	790.40 ± 44

[a]ADC value differences between control group and total patients with acromegaly.
[b]ADC value differences between control group and remission in patients with acromegaly.

value in the pre-motor cortex ($p = 0.001$) increased in Group 2 compared with those in the control group.

Figure 1 shows a macroadenoma on the pituitary gland and the ADC and FA measurements from different anatomical locations in a patient with acromegaly.

Among all patients with acromegaly, there was no significant correlation between time of hormone exposure, maximum ADC values (Pearson's correlation, 0.112; $p = 0.52$) and minimum FA values (Pearson's correlation, 0.201; $p = 0.24$).

DISCUSSION

Acromegaly is an insidious disease, which is often diagnosed late at about 4–10 years after its onset.[4] Clinical manifestations in each patient are different depending on the delay in diagnosis.[2] Acromegaly is a slowly progressive disease characterized by a 30% increase in mortality rate for cardiovascular disease and respiratory complications of malignancies. Patients with acromegaly generally exhibit coarsened facial features, acral enlargement, soft-tissue hyperplasia, carpal tunnel syndrome, visual abnormalities, headache and sleep apnoea.[1,17,18]

Serum IGF-1 levels adequately and uniformly reflect disease activity.[19] Long-standing exposure to IGF-1 and GH interferes with the regulation of trophic processes in many organ systems and is supposed to affect brain function and structures.[6] Several findings suggest that the GH has an important role during brain development.[9,20,21] GH and IGF-1 affect neurons, astrocytes and oligodendrocytes in several ways and play an essential role in neuronal cell proliferation, differentiation and myelination.[7,15,21–23] There are at least three different modes by which GH may affect brain function. The hormone may release secondary mediators from peripheral tissues, which, in turn, can cross the blood–brain barrier and affect the CNS. The second possibility is that GH may be enzymatically degraded to bioactive fragments, which may reach the CNS and act on peptidergic receptors. Finally, the hormone itself may enter the brain and directly affect areas responsive to GH.[8]

GH and IGF-1 affect centres related to appetite, cognitive functions, energy, memory, mood, neuroprotection, sleep and well-being.[8] Histological and genetic studies have shown that GH mRNA and IGF-1 are found in many centres in the brain, including predominantly in the hippocampus, parahippocampal areas, hypothalamus, amygdala, cerebellum, pre-frontal cortex, caudate nucleus, putamen, the striatum, thalamus and formation reticularis.[7,8,15] Also, serum IGF-1 levels were found to be positively correlated with cortical metabolism in the left pre-motor cortex and dorsolateral pre-frontal cortex.[24] IGF-1 stimulates the proliferation of the glial olfactory system and affects neuronal–axonal extensions.[25]

Table 2. Mean fractional anisotropy (FA) values of different brain regions in patients with acromegaly and control group

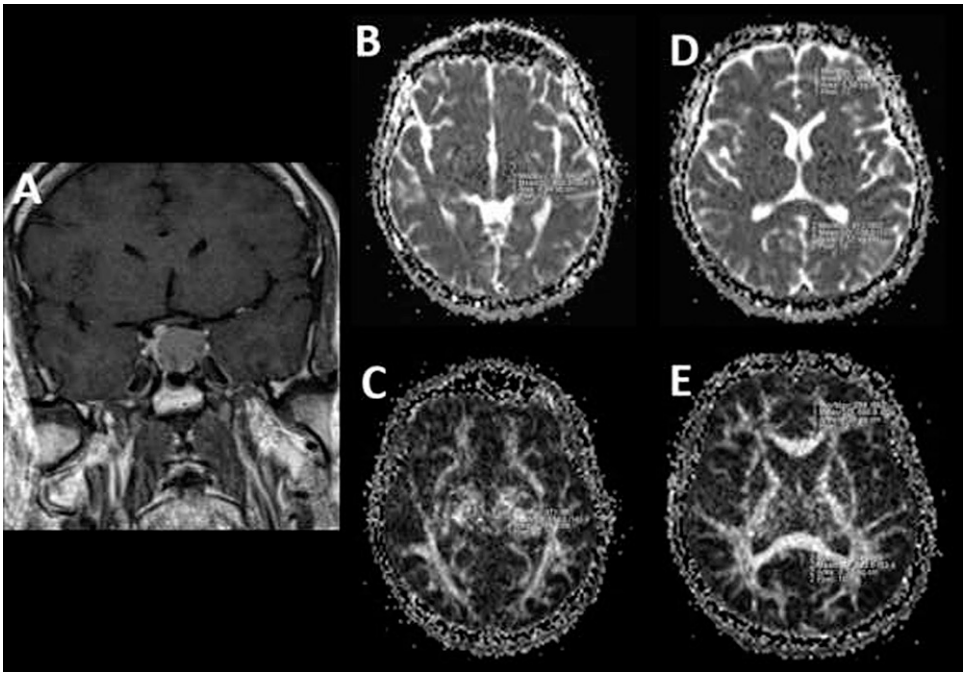
Locations	FA			
	Control ($n = 28$)	Non-remission ($n = 19$)	Remission ($n = 16$)	Total patients ($n = 35$)
Hypothalamus	$0.4 \pm 0.06^{a,b,c}$	0.4 ± 0.08	0.4 ± 0.05	0.4 ± 0.07
Thalamus	0.3 ± 0.04	0.3 ± 0.05	0.3 ± 0.05	0.3 ± 0.05
Caudate nucleus	0.2 ± 0.05	0.2 ± 0.04	0.2 ± 0.04	0.2 ± 0.04
Putamen	0.3 ± 0.04	0.3 ± 0.06	0.3 ± 0.06	0.3 ± 0.06
Genu of corpus callosum	0.8 ± 0.05	0.8 ± 0.04	0.7 ± 0.05	0.8 ± 0.05
Splenium of corpus callosum	0.8 ± 0.03	0.8 ± 0.04	0.8 ± 0.04	0.8 ± 0.04
Frontal white matter	0.3 ± 0.07	0.3 ± 0.02	0.3 ± 0.04	0.3 ± 0.03
Parietal white matter	0.4 ± 0.06^{c}	0.4 ± 0.06	0.4 ± 0.04	0.4 ± 0.05

[a]FA value differences between control group and remission in patients with acromegaly.
[b]FA value differences between control group and non-remission in patients with acromegaly.
[c]FA value differences between control group and total patients with acromegaly.

DTI provides microstructural information about biological tissues that is not available from other imaging techniques.[26,27] The clinical and scientific utility of DTI fibre tracking is found in both the localization and quantitative assessment of specific neuronal pathways, as applied to basic neuroscience.[28] ADC is a measurement of the rate of microscopic water motion without reference to any one direction, and FA is a measure of directionality affected by a number of factors, including development of parallel, compact fibre tracts as well as myelination.[29] FA assesses the degree of anisotropic diffusion occurring within a region. DTI is widely used in many neurological diseases, including cerebral ischaemia, multiple sclerosis, HIV, schizophrenia, head trauma and dementia, and in development and ageing research.[26]

There are a limited number of radiological studies on the effects of high hormone levels to the brain. Sievers et al[6] suggested that MRI examination should be used to show macroscopic brain alterations in acromegaly. By using conventional MRI, they showed that GH and IGF-1 increased grey matter and white

Figure 1. A 28-year-old female with acromegaly. The coronal T_1 weighted image with gadolinium (a) shows enhancing macroadenoma with stalk deviation in the pituitary gland. After selection and co-registration with the axial T_1 weighted images (not shown), the region of interest was transferred to apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps to measure ADC and FA values at the level of the hypothalamus [ADC measurement in (b) and FA measurement in (c)] and corpus callosum [ADC measurement in (d) and FA measurement in (e)].



matter volume.[6] They hypothesized that morphological changes in the brain occur during the first 10 years of hormone excess, and all of these effects on the brain are the result of the long-lasting exposure of neuronal or glial cells to systemically elevated hormone levels.[6,15,30] In another study using MRI, Sievers et al[5] found a decrease in the hippocampal volume in patients with acromegaly. They concluded that in addition to the neuropsychological tests, MRI could be used in the diagnosis of cognitive impairment.[5]

In the literature, the most important factors reported in the development of brain alterations are the elapsed time of diagnosis and control of disease. In this study, brain alterations were measured and followed by neurocognitive and psychiatric tests.[11] In acromegalic patients, we could not see any significant effect of duration and control of disease on brain diffusion metrics. Accordingly, we hypothesize that microstructural damage in the brains of patients with acromegaly occurs in the subclinical period before the diagnosis, as the brain has been already exposed to high hormone levels in this time period from 4 to 10 years.

Clinical and biochemical control is provided by decreasing the tumour size and controlling biochemical markers at normal levels. This situation is referred to as remission.[11]

In our study, the ADC value in the pre-motor cortex increased in patients in remission, which could represent vasogenic oedema with/without neuronal cell damage. This finding may explain how attention and memory that are associated with the pre-motor cortex are affected in acromegaly. We found decreased FA values in the hypothalamus of remission patients. The FA value in the hypothalamus decreased in non-remission patients. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland. Previous studies showed that the hypothalamus plays a role in the regulation mechanism of GH secretion.[8] The reduced FA values of the hypothalamus in both remission and non-remission groups indicate that fibre tracts could be damaged in this region; the mechanism of regulation has been corrupted, possibly as a result of this disruption, and acromegaly has occurred.

Structural brain changes are predictive of the degree of cognitive dysfunction, especially the involvement of the hippocampus is critical, since it plays a role in the memory and attention process.[5] The pre-frontal cortex is important for executive functions. In a study using positron emission tomography, a significant increase in cerebral blood flow was shown in the left pre-motor cortex and left dorsolateral pre-frontal cortex during working memory tests in high serum IGF-1 levels.[24] We demonstrated decreased FA values in the hypothalamus and parietal white matter in all patients with acromegaly. We thought that one of the most important mechanisms of brain tissue damage in acromegaly is the axonal and neuronal cell damage. Decreased FA values in different locations of the brain reflect fibre tract abnormality that is characterized by axonal damage, myelin integrity loss and the accumulation of inflammatory cells.

CONCLUSION

All patients with acromegaly showed brain diffusion alterations on DTI with no regard to disease duration and treatment status. There was no effect of disease duration on brain microstructural changes. Accordingly, we hypothesize that microstructural damage in the brain of patients with acromegaly occurs in the subclinical period before the diagnosis, since the brain has already been exposed to a high hormone level during this time period. No significant brain diffusion differences between remission and non-remission groups could lead us to think that the brain changes in patients with acromegaly might be irreversible. The use of DTI is feasible and accurate for the detection of brain changes in patients with acromegaly on both remission and non-remission groups.

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