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FULL PAPER

Relationships of DTI findings with neurocognitive dysfunction in children with Type 1 diabetes mellitus

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Objective: To determine whether there were diffusion tensor imaging (DTI) changes in the brain among children with Type 1 diabetes mellitus (DM) and investigate the correlation between the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values and neurocognitive functions.
Methods: 35 children with Type 1 DM and 21 age-matched healthy control subjects were included. Neurocognitive functions of subjects with Type 1 DM were evaluated. In both groups, FA and ADC values were calculated in 20 different locations. The association between neurocognitive function tests and FA and ADC values was investigated.
Results: Subjects with diabetes had significant changes in FA and ADC values in widespread brain regions compared with the healthy control group. ADC values in the caudate nucleus were negatively associated with verbal point. Increased ADC values in the genu of the corpus callosum were positively associated with Stroop test. There was a negative correlation between the ADC values of the parietal white matter and the judgment of line orientation test. FA values of the inferior longitudinal fasciculus were positively correlated with performance point. However, a negative correlation was noted between FA values of mid-brain and intelligence quotient level as well as another negative correlation between FA values of the posterior crus of the internal capsule and thalamus with verbal point.
Conclusion: Subjects with diabetes demonstrated significant changes in FA and ADC values in widespread brain regions, and such changes could be early features of injury to myelinated fibres or axonal degeneration. Our findings suggest that brain damage may have begun at the cellular level in the initial stage of Type 1 diabetes and neurocognitive impairments may be inevitable.
Advances in knowledge: DTI can demonstrate ADC and FA changes which are well correlated with neurocognitive dysfunction in the brains of children with Type 1 DM. This may help us in guiding preventive measures in early period of the disease before deterioration of neurocognitive functions.

INTRODUCTION

Diabetes mellitus (DM) Type 1 is a chronic metabolic disease developed in the childhood period resulting from autoimmune destruction of insulin-producing beta cells in the islets of Langerhans.[1,2] Clinical findings arise years after the occurrence of destruction to the beta cells. Identification and prevention of complications of Type I DM are as important as diagnosis and treatment of the disease.

The effects of Type 1 DM on developing central nervous system in children are controversial.[3] Previous studies with conventional MRI reported regional grey and white matter volume decrease in children with Type 1 DM.[4,5] A correlation was reported between some of these structural changes and the onset age of DM, levels of HbA1c, history of hypoglycaemia attack and the presence of retinopathy.[6–8] Some investigators detected hyperintense lesions in the white matter, increased cerebrospinal fluid volume, global cerebral atrophy, stable hippocampus and amygdala volume and decreased cerebral gray matter density in patients with Type 1 DM on MRI.[6,8–10]

Neurocognitive disorders are also lesser known complications of Type 1 DM. In earlier studies, adverse effects of DM, especially accompanying hypoglycaemia or hyperglycaemia, on the central nervous system and deterioration of several neurocognitive functions have been reported, but underlying pathophysiology is not well understood.[3,11–15] It has been speculated that abnormalities in the white matter of patients with Type 1 DM may be responsible for

cognitive dysfunction in these patients.[3] Kodl et al[14] reported that the existence of DM, particularly in the first years of life, may adversely affect the structural and functional development of the brain and lead to deterioration of neurocognitive functions including reduced performance on tests that measure working memory, learning, attention, information-processing speed and visual spatial memory.

Nowadays, new methods including MR spectroscopy, diffusion tensor imaging (DTI), single-photon emission CT and positron emission tomography for the diagnosis of white matter changes which lead to neurocognitive function disorders in patients with Type 1 DM are being developed. Sarac et al[16] reported metabolite changes in the parietal white matter and pons of children with Type 1 DM and concluded that this finding could be attributed to neuronal loss or neuronal dysfunction.

DTI is a unique technique suited to assess white matter microstructure.[17] It can provide recognition of tissue damage at microstructural level by measuring the magnitude and direction of the diffusion before the damage reaches a level that can be detected by conventional MRI. Fractional anisotropy (FA) allows us to evaluate the degree of anisotropic diffusion quantitatively. FA values are higher in white matters with a regular and organized structure such as the corpus callosum (CC), whereas FA values are lower in less regularly structured grey matter. Decrease in FA values is observed in situations such as white matter disintegration, axonal degeneration and axonal structural irregularity.[18] Previous studies performed with DTI have shown a correlation between the decreased FA values and neurocognitive impairment in various disorders including schizophrenia, depression, chronic alcoholism, Alzheimer disease and chronic drug abuse.[19] Apparent diffusion coefficient (ADC) is a measure of total degree of water diffusion within a tissue. Increased ADC values show the local cellular damage.

We used DTI to obtain quantitative data about brain structural integrity in different regions of the brain in subjects with Type 1 DM. We hypothesized that children with Type 1 DM will have changes in ADC and FA values, which will be correlated with neurocognitive dysfunction. The purpose of our study was to determine DTI properties of different brain regions in subjects with Type 1 DM, and to evaluate whether there was a correlation between DTI findings and neurocognitive functions.

METHODS AND MATERIALS

Subjects

A total of 35 children (Group 1) (20 females, 15 males; age range, 9–15 years; mean age 12.6 ± 1.9 years), previously diagnosed with Type 1 DM based on standard clinical and laboratory criteria, with normal neurological examination were enrolled in this study. Children with predetermined neuropsychiatric disorders such as autism and obsessive compulsive disorder or comorbid chronic diseases other than Type 1 DM were excluded from the study. Control group (Group 2) included 21 healthy children (12 females, 9 males; age range, 8–15 years; mean age 11.4 ± 2.4 years) with normal neurological examination, clinical and laboratory findings.

All subjects reported to our radiology department for cranial MRI during the post-prandial period (within 2 h after breakfast or lunch). On a separate day but within 10 days after cranial MRI, subjects reported to the child psychology department for neurocognitive testing during the post-prandial period (within 2 h after breakfast or lunch). Upon arrival, the blood glucose levels of subjects were measured from their fingertip blood by their own manual device before MRI examination or neurocognitive testing. To standardize the study, subjects with blood glucose levels between 100 and 250 $\mathrm{mg\,dl^{-1}}$ were taken into our routine study protocol. We know that hypoglycaemia or hyperglycaemia may lead to acute diffusion changes in the brain and alter neurocognitive situation; therefore, subjects with glucose levels outside of this range were re-evaluated after 1 h or were given an appointment for another day again. Parameters including sex, age and body mass index were recorded in all subjects enrolled in this study. Subjects' parents were queried about duration of diabetes, family history, episodes of diabetic ketoacidosis (DKA) and/or hypoglycaemia. 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. All subjects' parents were fully informed and gave their written informed consent.

Imaging technique

MRI was performed on a 1.5-T system (Avanto; Siemens Medical Solution, Erlangen, Germany) using head coil. Before MRI examination, information was given about the procedure to the children and their parents. In none of the patients intravenous contrast material and drugs for sedation were used. First, routine brain imaging with T_1 weighted three-dimensional magnetization-prepared rapid-acquisition gradient-echo [repetition time (TR)/echo time (TE)/inversion time, 12.5/5/450 ms; matrix 128×128; field of view (FOV), 200×230 mm], T_2 weighted spin-echo (TR/TE, 4530/100 ms; matrix, 128×128; FOV, 200×230 mm) and fluid-attenuated inversion-recovery images (TR/TE/inversion time, 800/90/2500 ms; matrix 128×128; and FOV, 230×230) were obtained, and then, DTI sequence was applied. The DTI protocol consisted of a single-shot, spin-echo, echo-planar sequence with fat-suppression technique: TR/TE, 2700/89 ms; matrix, 128×128; FOV, 230×230 mm; and slice thickness, 3 mm. 30 diffusion-encoding directions were used at $b = 0\,\mathrm{s\,mm^{-2}}$ and $b = 1000\,\mathrm{s\,mm^{-2}}$. The entire brain was imaged. A high-resolution whole-brain T_1 weighted image, with the same slice thickness, was used to register the tensor data to structural volumes. The Leonardo console (software v. 2.0; Siemens) was used for ADC and FA map reconstruction.

In both groups, 20 distinct neuroanatomic locations that have been previously suggested to be to related to cognitive function and affected by diabetes were selected for the analysis: the cingulum, superior longitudinal fasciculus, genu and splenium of CC, anterior and posterior limbs of internal capsule, caudate nucleus, putamen, globus pallidus, inferior longitudinal fasciculus, corticospinal tracts at anterior mid-brain and pons, central tegmental tracts at posterior mid-brain and pons, cerebellar white matter, hypothalamus, frontal white matter, posterior parietal white matter and corona radiata.[19–23] To standardize the

measurements, all regions of interest (ROIs) were obtained from the left side. T_1 weighted three-dimensional magnetization-prepared rapid-acquisition gradient-echo and T_2w images were used as anatomic references for the placement and tracing of ROIs. These images were coupled with the corresponding region of ADC and FA maps at the same section level. Two experienced radiologists (HT and HY), who were blinded to clinical conditions of the subjects, manually drew similar-size ROIs on axial colour-encoded ADC and FA maps of all subjects (Figures 1 and 2). The sizes of ROIs were $8\,mm^2$ in the cingulum, superior longitudinal fasciculus, inferior longitudinal fasciculus, genu of CC, anterior and posterior limbs of internal capsule, corticospinal tracts at anterior mid-brain and pons, central tegmental tracts at posterior mid-brain and pons; $15\,mm^2$ in the splenium of the CC, putamen and globus pallidus; and $20\,mm^2$ in caudate nucleus, thalamus, cerebellar white matter, hypothalamus, frontal white matter, posterior parietal white matter and corona radiata. ADC and FA values were obtained automatically with reference to corresponding ADC and FA maps. We minimized partial-volume effects by inspecting the slices above and below the region to avoid averaging with the cerebrospinal fluid.

Neurocognitive testing

To evaluate neurocognitive functions, WISC-R scale (revised form of Wechsler intelligence scale for children), Stroop test, number sequences test and judgment of line orientation test were performed. WISC-R and other neurocognitive tests were performed by a child psychologist (MF) in two sessions 1 week apart and recorded. Neurocognitive tests lasted approximately between 2 and 2.5 h. WISC-R scale is composed of two sections (verbal and performance). The verbal section includes six subtests (general information, similarities, comprehension, vocabulary, number sequence, arithmetic), and the performance section includes six subtests (picture completion, picture arrangement, block design, part uniting, cipher encoding and labyrinths). Following the completion of the WISC-R test the verbal intelligence coefficient, performance intelligence coefficient and total intelligence quotient (IQ) coefficient were obtained. The validity and reliability of the WISC-R scale was ascertained by Savasir and Sahin in Turkish children.[24] Stroop test measures attention. With Stroop test, points of failure, points of correction and completion time can be measured. Number sequences test measures learning ability. Number sequences test contains number sequences which are given as finite sequences of numbers in certain patterns. Judgment of line orientation test developed by Benton measures visual perception.[25] The validity and reliability of Stroop test, number sequences test and judgment of line direction test have been done by Karakas and Dincer in Turkish children.[26] In this study, neurocognitive function tests had not been performed in normal children because these tests took a long time. So, standard values reported for normal healthy subjects by Savasir and Sahin and Karakas and Dincer were used for comparison between the two groups (subjects with Type 1 DM and healthy control group).[24,26]

Statistical analysis

All statistical analyses were performed using a commercially available SPSS® release 20.0 software package (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The results were presented as mean ± standard deviation. In statistical analysis, all quantitative variables were compared by independent *t*-test for normal distributed variables in two groups. Manova test was also used to compare these variables to adjust their interaction. Spearman correlation was used to evaluate all correlations within groups. Two-tailed p values <0.05 were accepted as statistically significant.

RESULTS

Demographic data

The mean duration of disease was 3.3 ± 2.5 years, mean HbA1c value was $8.9 \pm 2.4\,mg\,dl^{-1}$ and average onset age of the disease was 9.2 ± 3.1 years. 15 patients with Type 1 DM had a history of DKA attack, and other 9 patients had a history of hypoglycaemia attack.

DTI data and comparison of FA and ADC values obtained from 20 different locations in Group 1 and Group 2 (healthy controls)

The mean FA and ADC values of each group are summarized in Table 1. There was a significant difference in FA values of the putamen, inferior longitudinal fasciculus, thalamus, corticospinal tracts at pons, frontal white matter, hippocampus and corona radiata between two groups. FA values of Group 1 were

Figure 1. Fractional anisotropy (FA) values at the genu of corpus callosum, caudate nucleus and splenium of corpus callosum (a, circles) and at the cingulum (b, circles).

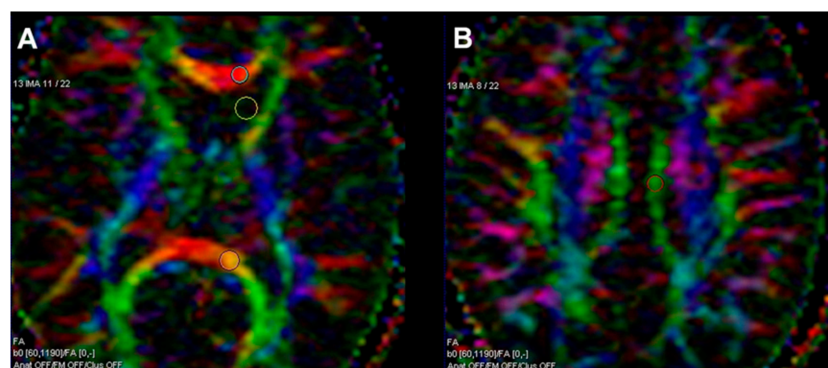
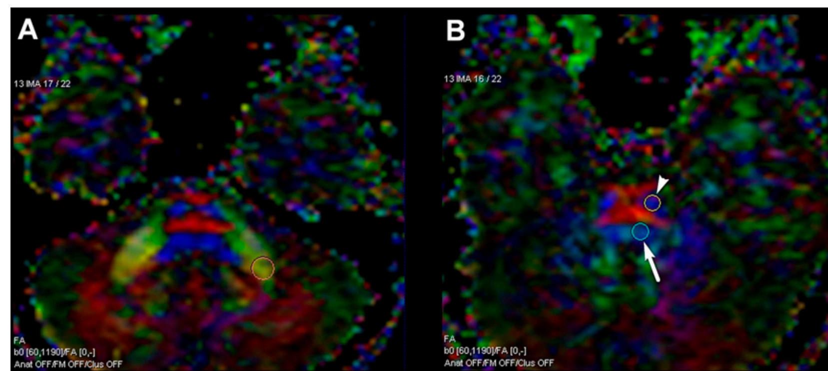


Figure 2. Regions of interest defined on a fractional anisotropy (FA) image at the cerebellar white matter (a, circles) and mid-brain level (b). arrow head: corticospinal tracts; white arrow: central tegmental tracts.



significantly lower than that of Group 2 ($p = 0.00001$, $p = 0.001$, $p = 0.00001$, $p = 0.009$, $p = 0.002$, $p = 0.00001$ and $p = 0.007$, respectively). ADC values of central tegmental tracts at the mid-brain and corona radiata were higher in Group 1 than those in Group 2 ($p = 0.001$, $p = 0.002$, respectively).

Correlation between FA and ADC values obtained from different locations and neurocognitive function tests

In subjects with DM Type 1, a significant negative correlation was detected between the verbal point and FA values of the

Table 1. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of different brain regions in subjects with Type 1 diabetes mellitus and control group are given

Locations	Group 1 ($n = 35$)		Group 2 ($n = 21$)	
	FA	ADC	FA	ADC
Cingulum	513.94 ± 73	779.46 ± 68	578.43 ± 83	803.29 ± 68
AL internal capsule	521.49 ± 65	740.4 ± 47	581.9 ± 79	766.81 ± 51
PL internal capsule	676.34 ± 49	755.6 ± 45	696.95 ± 58	758.71 ± 45
Caudate nucleus	208.46 ± 35	745.09 ± 64	228.33 ± 39	772.48 ± 33
Genu CC	827.37 ± 55	769.97 ± 75	825.52 ± 38	804.71 ± 75
Splenium CC	828.2 ± 54	785.06 ± 77	834.95 ± 40	800.14 ± 60
Globus pallidus	301.17 ± 53	811.06 ± 55	333.19 ± 46	832.38 ± 62
Putamen	176.57 ± 26	757.09 ± 26	223.05 ± 26	768 ± 39
SLF	527.34 ± 70	767.34 ± 59	535.57 ± 92	742.81 ± 67
ILF	557.46 ± 72	833.51 ± 63	625.81 ± 60	849.9 ± 56
Thalamus	296.8 ± 45	800.11 ± 48	364.43 ± 52	801.62 ± 49
CST (mid-brain)	649.09 ± 82	780.46 ± 67	680.57 ± 79	730.9 ± 65
CTT (mid-brain)	600.11 ± 79	835.14 ± 59	629.86 ± 81	772.9 ± 77
CST (pons)	521.31 ± 75	734.2 ± 55	574.33 ± 62	746.29 ± 55
CTT (pons)	611 ± 70	835.57 ± 56	598.71 ± 48	836.62 ± 66
CWM	584.71 ± 60	711.23 ± 39	593.52 ± 61	692.76 ± 41
FWM	342.31 ± 69	792.51 ± 39	397.38 ± 49	792.14 ± 54
PWM	559.49 ± 69	738.86 ± 51	541.86 ± 85	738.81 ± 51
Hypothalamus	157.71 ± 40	903.77 ± 47	234.67 ± 51	890 ± 64
Corona radiata	479.37 ± 77	779.8 ± 49	538.86 ± 73	777.95 ± 57

AL, anterior limb; CC, corpus callosum; CST, corticospinal tracts; CTT, central tegmental tracts; CWM, cerebellar white matter; FWM, frontal white matter; ILF, inferior longitudinal fasciculus; PL, posterior limb; PWN, parietal white matter; SLF, superior longitudinal fasciculus.
Group 1: subjects with Type 1 diabetes mellitus, Group 2: control group.

posterior limb of the internal capsule and thalamus ($r = -0.426$, $p = 0.011$ and $r = -0.358$; $p = 0.035$, respectively).

There was a negative correlation between the ADC values of the caudate nucleus and verbal point ($r = -0.338$, $p = 0.047$). A positive correlation scores between the ADC values of the genu of the CC and Stroop test was found ($r = 0.384$, $p = 0.023$).

There was a positive correlation between the FA values of inferior longitudinal fasciculus and performance point ($r = 0.355$, $p = 0.037$).

There was a negative correlation between IQ level and FA values of central tegmental tracts at mid-brain level ($r = -0.354$, $p = 0.037$).

A negative correlation was found between the ADC values of the parietal white matter and judgment of line direction test ($r = -0.366$, $p = 0.031$).

DISCUSSION

Increased FA values reflect a higher degree of white matter integrity, but this depends on the local architecture of the white matter.[27] In a study using DTI performed in adult patients with Type 1 DM, FA values in different brain regions were found to be lower. They hypothesized that axonal damage or loss of coherence in fibre bundles is an early process in Type 1 DM.[20] In our study, decreased FA values in the putamen, inferior longitudinal fasciculus, thalamus, corticospinal tracts at pons, frontal white matter, hippocampus and corona radiata were detected. While FA reflects a complex involvement of tissue properties, including compatibility of fibre orientation, myelination and axonal density, decreased FA values in our study may suggest white matter disintegration, axonal degeneration and axonal structural irregularity. In the present study, no FA changes were present in the parietal region. Barnea-Goraly et al[22] reported that younger age onset of DM was associated with widespread lower FA values including the parietal region. They hypothesized that young children are especially susceptible to brain insults resulting from conditions of Type 1 DM such as chronic hyperglycaemia, hypoglycaemia and acute hypoglycaemic complications. Aye et al[21] reported lower axial diffusivity (AD) in the temporal and parietal regions in children with Type 1 DM. AD is a measure of water diffusivity along the main axis of diffusion within a voxel and reflects the fibre coherence and structure of axonal membranes.[22] Aye et al explained this lower AD with less axonal coherence in these brain regions. Absence of FA changes in the parietal region in our study may be explained by the late onset of diabetes in our study population compared with two other studies.[21,22] We thought that in the late onset of Type 1 DM, white matter microstructural changes may not be present.

Barnea-Goraly et al[22] showed a positive correlation between IQ levels and FA values of the superior temporal gyrus and parietal white matter. Their findings can be attributed to processes related to hyperglycaemia and glucose variability targeting myelin and resulting in reduced FA. Contrary to their study, we did not find any correlation between IQ levels and FA values of the superior temporal gyrus and parietal white matter; but, we detected a negative correlation between the IQ level and FA values of central tegmental tracts at mid-brain level. In addition, we also found a negative correlation between the decrease in verbal test score and FA values of the posterior limb of the internal capsule and thalamus. In areas comprising pathways of intersecting fibres (*e.g.* pons and mid-brain), degeneration affecting fibres of one direction may lead to paradoxical increase in FA. This paradoxical increase in FA has been reported by Pierpaoli.[28] Aye et al[21] reported reduced radial diffusivity (RD) in the thalamus. Thalamus is a region that may be affected by conditions associated with Type 1 DM including hyperglycaemia and ketoacidosis.[4,29,30] RD is the mean of the diffusivities perpendicular to the vector with the largest eigenvalue and reflects the degree of myelination.[5] Axonal degeneration and demyelination will increase RD. In general, there is an inverse relation between RD and FA.[22] The increased FA values in the thalamus in our study may reflect secondary injury owing to the disruption of white matter tracts connecting these structures to other brain regions.

In this present study, a positive correlation was found between the FA values of the inferior longitudinal fasciculus and performance point. Subjects with decreased FA values at the inferior longitudinal fasciculus also had lower performance point. This finding may indicate injury to these fibre tracts.

While other studies reported no difference in FA values of the hippocampus between patients with Type 1 DM and the healthy control group, FA values of the hippocampus were significantly lower in the group with diabetes than in the control group in our study.[21,23] Antenor-Dorsey et al[23] found increased mean and RD in the hippocampus associated with hyperglycaemia attack. Mean diffusivity (MD) is an inverse measure of the membrane density and sensitive to cellularity, oedema and necrosis.[31] We did not calculate other DTI measures including AD, RD and MD, but lower FA values in the hippocampus can be attributed to axonal degeneration and demyelination. Hippocampus, a precise anatomic location, is very sensitive to episodes of hypoglycaemia, ischaemia and hyperglycaemia.[21,23] In the hippocampus of subjects with diabetes, an irreversible damage may begin owing to poor glycaemic control and frequent hypo/hyperglycaemia attacks in early period of the disease.

Franc et al[32] reported reduced FA values in optic radiations, the posterior corona radiata and CC splenium. Similarly, we found lower FA values and higher ADC values in the corona radiata. The possible explanation for low FA values is that myelinated fibres were affected, and even relatively high ADC levels show that irreversible damage had begun. We suggested that myelinated fibres may be affected earlier than it was thought.

In the present study, we also detected increased ADC values in the genu of the CC in subjects with high error score in Stroop test, which measures selective attention. The genu of the CC is an important cognitive domain.[33] This finding may support the opinion that damage to the anterior part of CC may be associated with neurocognitive dysfunction. Kodl et al[19] reported decreased FA values in the CC splenium in middle-aged subjects with Type 1 DM. However, any significant difference has not

been identified between FA values of the CC genu and splenium in our present study. We speculated that in the early period of disease in paediatric population, the posterior part of the CC had not been affected yet.

The present study has some limitations. First, neurocognitive tests were not performed in the control group. Standard values reported for normal healthy subjects in the Turkish population reported in the literature were used for comparison. Second, we had only once timed HbA1c level of patients. Third, we evaluated only FA and ADC values, but we did not take into account other DTI parameters including AD, RD and MD.

Brain microstructural changes and neurocognitive dysfunction reported in subjects with diabetes likely begin in childhood period. An association between early age of onset of diabetes (generally in the first decade of life) and neurocognitive dysfunction has been a well-known finding in the literature.[21,23,34,35] DKA attacks, chronic hyperglycaemia and blood glucose fluctuations all may negatively affect brain development, which results in neurocognitive dysfunction in young children with Type 1 DM.[21,23,35]

CONCLUSION

Type 1 DM may result in microstructural changes at an early stage of the disease, and consequently, this may lead to impairments in neurocognitive functions in the childhood period. We can speculate that conditions of Type 1 DM such as chronic hyperglycaemia, hypoglycaemia and acute hypoglycaemic complications may result in ADC and FA changes. DTI can demonstrate these changes which are well correlated with neurocognitive dysfunctions. Broader and longer term advanced neuroimaging studies will help us in understanding the likely effects of DM on the brain and will help us in guiding preventive measures in the early period of the disease before deterioration of neurocognitive functions.

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