Analysis of diabetes-related cerebellar changes in streptozotocin-induced diabetic rats

Nuriye Güzin ÖZDEMİR1*, Feray AKBAŞ2, Tuğba KOTİL3, Adem YILMAZ4
1Neurosurgery Clinic, İstanbul Training and Research Hospital, İstanbul, Turkey
2Internal Medicine Clinic, İstanbul Training and Research Hospital, İstanbul, Turkey
3Histology and Embryology Department, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
4Neurosurgery Clinic, Şişli Etfal Training and Research Hospital, İstanbul, Turkey

1. Introduction
Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia, leading to damage in a number of tissues. Retinas, neurons, and kidneys are especially affected (1). Acute and chronic complications may occur. Chronic complications are divided into vascular and nonvascular complications. Vascular complications are subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease, cerebrovascular disease). Oxidative stress, glycosylation, and protein kinase-C activation are shown in all tissues affected by microvascular complications (1–3). Glucose homeostasis in humans is important for the functioning of the nervous system. The brain is an insulin-sensitive organ with widespread and selective expression of the insulin receptor in the olfactory bulb, hypothalamus, hippocampus, amygdala, cerebral cortex, and cerebellum; hypoglycemia and hyperglycemia affect the central and peripheral nervous system, leading to severe dysfunction (1–3). Chronic hyperglycemia is associated with functional and structural blood–brain barrier (BBB) changes in cerebral microvessels (3). Diabetes is also associated with gradually developing end-organ damage in the central nervous system, known as diabetic encephalopathy, characterized by impairment of cognitive functions and electrophysiological changes. Chronically increased intracellular glucose concentration leads to functional, structural, and neurodegenerative changes (1).

2. Materials and methods
Twenty male adult Sprague Dawley rats weighing 200–220 g were obtained from the Experimental Medicine Research Institute (DETAE). Fourteen of these animals were selected as the diabetic group, and after 12 h of
fasting they underwent a single intravenous injection of 65 mg/kg STZ dissolved in 0.9% NaCl. The remaining 6 rats constituted the healthy control group. During the first two days following the injection, all animals were kept in equal environmental conditions. On the second day, all rats injected with STZ were checked for the induction of diabetes by assessment of blood glucose levels in the tail vein using a glucometer (Rheamed, Sand County Biotechnology, Inc., Taiwan). Animals with fasting blood glucose levels above 200 mg/dL were accepted as diabetic. Three rats were excluded from the diabetic group due to blood glucose levels under this value.

All animals were kept in standard rat cages with two animals in each cage, at 21 ± 2 °C and a 12/12 light/dark cycle. They were given standard rat pellet and water ad libitum.

Blood glucose levels of the control group were evaluated at the same time as the diabetic group to confirm normoglycemia (60–100 mg/dL). Three rats from the diabetic group died during the study.

After 21 days, all 14 rats (8 diabetic and 6 control) that completed the study were sacrificed under ether anesthesia. They were decapitated, their cerebellums were removed with dissection, and histological sections were obtained for the electron microscopic study.

For electron microscopic study, tissues were fixed using 2.5% glutaraldehyde (Fluka-49630) at 4 °C and secondary fixation was done using 1% osmium tetroxide (EMS-19134) for 1 h at 4 °C. After washing with phosphate-buffered saline, tissues were treated with 1% uranyl acetate at 4 °C for 1 h. After an ascending acetone (Riedel-de Haen-24201) series (30%, 50%, 70%, 90%, 100%, 100%) tissues were treated with 1:1 acetone:epon, 1:3 acetone:epon, and pure epon at room temperature for 1 h and then embedded in capsules filled with pure epon (Fluka 45359). The polymerization capsules were incubated at 60 °C for 18 h. Semithin (0.5 µm) and thin (0.06 µm) sections of tissue samples were cut by ultramicrotome (Leica EM UC7, Wetzlar, Germany). Semithin sections were taken and stained with toluidine blue and evaluated under light microscope. Thin sections were placed on a nickel grid and stained with drops of uranyl acetate for 30 min and a drop of lead nitrate for 6 min. Sections were evaluated under a JEOL JEM 1011 transmission electron microscope (Peabody, MA, USA). The images were transferred to the Soft Imaging System Analysis program (Olympus, Tokyo, Japan) with a Megaview III digital camera (Olympus) and pictures were taken.

Mitochondrial area and smooth endoplasmic reticulum (SER) tubules and rough endoplasmic reticulum (RER) cisternae diameters were counted in 50 random areas from each group using 20,000× magnification in the Soft Imaging System Analysis program using a Megaview III. The results were analyzed statistically using GraphPad software (San Diego, CA, USA) and graphs were plotted using Excel software (Microsoft, Redmond, WA, USA).

This study was approved by the DETAE Ethics Committee.

3. Results
Blood glucose levels and initial and final body weights of the rats are shown in Tables 1 and 2.

In the histopathologic examination, the layers of the cerebellum were examined using light and electron microscopy.

In light microscopy, all layers (molecular, ganglionic, and granular) showed intact morphology in the control group (Figures 1A and 1B). However, in the diabetic group, the nerve fibers and glial cells in the molecular and granular layers had spaces between them. There were wide edematous areas around the Purkinje cells forming the ganglionic layer. In addition to normal-appearing Purkinje cells, sections showed dark colored cells having picnotic nuclei and harboring vacuoles in their cytoplasm. Nerve fibers in the white substance did not show integrity (Figures 1C and 1D).

<table>
<thead>
<tr>
<th>Rat number:</th>
<th>Weight (initial) (g)</th>
<th>Weight (final) (g)</th>
<th>BS (initial) (mg/dL)</th>
<th>BS (final) (mg/dL)</th>
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<td>6</td>
<td>288</td>
<td>328</td>
<td>96</td>
<td>125</td>
</tr>
<tr>
<td>Mean ± standard deviation</td>
<td>289 ± 11</td>
<td>314 ± 10</td>
<td>90 ± 7</td>
<td>114 ± 20</td>
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</table>
Table 2. Diabetic group: weight and blood sugar (BS) values of the animals, initially and finally.

<table>
<thead>
<tr>
<th>Rat number</th>
<th>Weight (initial) (g)</th>
<th>Weight (final) (g)</th>
<th>BS (initial) (mg/dL)</th>
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<td>8</td>
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<td>479</td>
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<td>Mean ± standard deviation</td>
<td>301 ± 17</td>
<td>243 ± 33</td>
<td>289 ± 46</td>
<td>408 ± 49</td>
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Figure 1. A, B: Semithin sections of the control group. All three layers (molecular (M), ganglionic (Gn), and granular (G)) are intact. C: Semithin sections of the diabetic group. Edematous areas (asterisks) were seen between the nerve fibers and glial cells in the molecular and granular layers and around Purkinje cells forming the ganglionic layer. D: In addition to normal-appearing Purkinje cells, diabetic sections showed dark colored cells (black arrows). (Toluidine blue; 20×)
Results of the electron microscopic study were stated as layers, myelin structures, and vascular structures.

3.1. Molecular layer
Electron microscopy of the thin sections in the control group showed that the dendrites of the Purkinje cells in the molecular layer were separated from the parallel fibers of the granular cells surrounding them by a prominent plasma membrane (Figure 2A). Purkinje cell dendrites in the molecular layer of the control group had intact mitochondria with prominent cristae in their cytoplasms, RER cisternae parallel to each other, SER tubules, and prominent neurofilaments (Figure 2B). Nerve fibers of the granular cells were elongated into the molecular layer and the membranes of the dendritic elongations were intact and had normal SER content.

In contrast to the control group, in the diabetic group there were dilated endoplasmic reticulum tubules in the dendrites of the Purkinje cells (Figure 2C). Parallel fibers belonging to the granular cells next to Purkinje cell dendrites, and the dendritic tips adjacent to them, had excessive edema and widening, ruptures in the membranes, and widening in their SER tubules (Figure 2D).

In the control group, glial cells were rarely observed in the molecular layer and had a nuclear membrane that possessed euchromatic genetic material and a prominent nucleus. These cells had prominent plasma membranes, and also had mitochondria with abundant cristae, free ribosomes, and RER and SER cisternae (Figures 3A and 3B).

Figure 2. Electron microscopy micrograph from molecular layer of the control group. A: The dendrites of the Purkinje cells found in the molecular layer have intact plasma membrane (black arrows) (5000×). B: Well-organized SER tubules, parallel RER cisternae, clear neurofilaments (red arrows), and mitochondria were seen in the cytoplasm of dendrites (15,000×). C and D: Electron microscopic micrograph from molecular layer of the diabetic group: excessive edema and widening in the fibers of the granular cells adjacent to the Purkinje cell dendrites, and also in the dendritic tips next to them (red arrows). There are dilated SER tubules (black arrows) in the dendrites (7500×, 12,000×). pf: parallel fibers, D: dendrite, m: mitochondria, ser: smooth endoplasmic reticulum, rer: rough endoplasmic reticulum.
In the diabetic group, when the glial cells in the molecular layer were examined, mitochondria showed cristae loss and swelling (Figures 3C and 3D).

3.2. Purkinje layer

In the control group, the Purkinje cells were surrounded by a prominent plasma membrane, and the nuclear membrane circumscribing their euchromatic genetic material was intact and prominent. In the giant cytoplasms of Purkinje cells, parallel aligned cisternae of RER and well-organized tubules of SER and numerous mitochondria with clear cristae were detected (Figures 4A–4D).

In the diabetic group, Purkinje cells were decreased in size and exhibited extreme invagination in the plasma membrane, extreme darkening in the cytoplasm and nucleus, prominent round nucleolus within the puckered nucleus, swelling and loss of cristae in the mitochondria, and dilated SER tubules and RER cisternae. There was also swelling in the vesicles that composed the Golgi apparatus, and there were multivesicular bodies (Figures 5A–5D).

The diameters of RER cisternae (50.86 ± 0.9 nm) and SER tubules (75.42 ± 2.2 nm) of the control group and the diameters of RER cisternae (169.93 ± 1.5 nm) and SER tubules (194.30 ± 1.4 nm) of the diabetic group showed extremely significant differences (P < 0.0001) (Figure 6). Moreover, swelling of the mitochondria of Purkinje cells between the two groups was compared by measuring the area of mitochondria. The data showed extremely significant difference between the two groups (control: 195,368 nm²; diabetes: 388,426 nm²) (P < 0.0001) (Figure 7).

Golgi type II cells adjacent to the Purkinje cells were distinguished from the immediately underlying granular cells by the bigger dimensions of the former. Golgi type II cells had a round nucleus with euchromatic material and the nuclear membrane was prominent. They also had free ribosomes, mitochondria, Golgi apparatus, and small SER tubules (Figure 8A).

Figure 3. A and B: Glial cells in the molecular layer of the control group have intact mitochondria with prominent cristae in their cytoplasms (10,000×, 15,000×). C and D: In the diabetic group, swelling and cristae loss in the mitochondria were detected in the glial cells of the molecular layer (10,000×, 20,000×). N: nucleus, m: mitochondria, rer: rough endoplasmic reticulum.
In the diabetic group, Golgi type II cells adjacent to the Purkinje cells had severe edema that would harm all the cytoplasmic content (Figures 8 B–8D).

3.3. Granular layer
In the control group, the nuclear membranes of the normal granular cells and the plasma membrane between neighboring granular cells had distinct borders. The nuclei of granular cells included marginal heterochromatic clusters, while in the center it was euchromatic. The morphology of the cytoplasmic content resembled Golgi cells showing normal morphology (Figures 9A and 9B).

In the diabetic group, invaginations of the nuclear membranes of the granular cells and loss of circular appearance were seen. There was damage to the mitochondria and widening in the endoplasmic reticulum was detected. Some cells in the granular layer had extreme nuclear condensation, which is a sign of apoptosis (Figures 9C and 9D).

3.4. Myelin sheath
In the control group, the neuropil that surrounded the cells of the granular layer had synaptic connections between the nerve fibers, a normal mitochondrial morphology, and a normal structure of the synaptic vesicles. The myelinated nerve fibers, which were present in all the layers of the gray substance and constituted the white substance, had intact myelin sheaths, and the mitochondria and neurofilaments within the nerve fibers had normal morphology (Figure 10A).

In the diabetic group, the myelin sheath of the nerve fibers had local or diffuse separations and breaks. Mitochondria inside the nerve fibers were damaged due to loss of cristae (Figures 10B–10D).

3.5. Vascular structures
In the control group there were normal endothelial cells with pericytes around them (Figure 11A).

In the diabetic group, the basal lamina was thick and
Figure 5. A–D: Electron micrographs of the Purkinje cells from ganglionic layer of the diabetic group. Swelling and loss of cristae in the mitochondria, dilated RER cisternae and SER tubules were seen in the dark Purkinje cells (6000×, 20,000×, 20,000×, 20,000×). N: nucleus, ser: smooth endoplasmic reticulum, m: mitochondria, rer: rough endoplasmic reticulum.

Figure 6. The mitochondria area of Purkinje cells in the control and diabetes groups. Extremely significant differences control versus the diabetes group (*P < 0.0001).
Figure 7. SER and RER diameters of Purkinje cells in the control and diabetes groups. Extremely significant differences versus diabetes group (*P < 0.0001).

Figure 8. A: Electron micrograph of the control group. Golgi type II cells (arrows) have a round nucleus with euchromatic material and the nuclear membrane is prominent (5000×). B–D: Electron micrograph of the diabetic group. Golgi type II cells (arrows) have severe edema and loss of organelles (asterisks) (5000×, 10,000×, 12000×). N: nucleus, PC: Purkinje cell, m: mitochondria.
irregular, and splitting of the lamina densa was detected. Moreover, degenerative changes in the cytoplasms of the pericytes adjacent to the blood vessel and edema in the astrocyte elongations next to the vessels were observed (Figures 11B–11D).

4. Discussion
DM is a metabolic disorder leading to serious consequences in insulin-sensitive organs such as the retinas, kidneys, and neurons. The brain is regarded as an insulin-sensitive organ with expression of the insulin receptor in the olfactory bulb, hypothalamus, hippocampus, cerebellum, amygdala, and cerebral cortex (1,3).

While the effects of diabetes on the peripheral nerves are better known, there is less information on the cerebral cortex. Data on cerebellar changes are even more limited and less studied. Previous studies reported that structural and ultrastructural brain changes were accompanied by depression in diabetic rats. The cerebral cortex, cerebellum, and hypothalamus have been shown to be involved in depression (1,3). However, all these studies are not specific to the cerebellum. Research studies related to the cerebellum are very few to our knowledge (1,2,4,7,8).

Diabetes exacerbates neuronal injury induced by hyperglycemia-mediated oxidative damage. Brain neuropathy is observed as alterations of myelin in different regions of the brain. Increased myelin alterations are observed in the cerebral cortex of diabetic rats. The myelin disarrangement is the result of decreased myelin-associated glycoprotein, autoantibodies to myelin basic protein, myelin damage induced by nitric oxide, impairment of oligodendrocyte function, and inhibition of Schwann cell proliferation. Synaptic transmission is changed due to axonal synaptic bouton swelling (1,2,7). We observed that the myelin sheath of the nerve fibers had local or diffuse separations and breaks.

Figure 9. A: General appearance of granular cells in the control group (5000×). B: The plasma membrane between neighboring granular cells of the control group is clear (arrows) (12,000×). C: Invaginations (arrows) of the nuclear membrane, loss of cristae in mitochondria, and dilated SER tubules were seen in the diabetic group (20,000×). D: In the diabetic group, nuclear condensation of the granular cells as a sign of apoptosis (arrows) (12,000×). N: nucleus, m: mitochondria, ser: smooth endoplasmic reticulum, E: edema.
Oxidative and nitrosative stress in diabetic rats also leads to progressive mitochondrial structural changes and the apoptotic process begins, leading to secondary cell death in diabetes (9). However, the presence of normal mitochondria besides swollen and vacuolated ones suggests that either a mitochondrial compensatory mechanism or a selective mitochondrial resistance could be present (7,8). We found degenerative changes in all the layers of cerebellum, in addition to myelin and vascular changes. Mitochondrial structural, axonal, synaptic, and apoptotic alterations, as well as structural degenerative changes in all the cell organelles, were seen. We also observed crista loss and multilamellar changes of the mitochondrial structures in molecular and Purkinje cell layers as well as unchanged mitochondria.

Antioxidant marker enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and glutathione were markedly decreased, and there was an increase in malondialdehyde in a study in STZ-induced diabetic rats (10).

Enhanced expression of the mitochondria-specific stress protein chaperonin 60 and the oxidative stress protein MnSOD at the protein level has been reported in the CA1/CA3 region of the hippocampus of STZ-induced diabetic rats after 7 weeks (1).

A histologic structural study to observe the effect of STZ-induced DM on the cerebellar cortex of adult rats showed degenerative changes in neurons, mitochondrial alterations, and disarrangement of myelin sheaths, with increased area of myelinated axons. In addition, separated presynaptic vesicles in swollen axonal terminals and a significant increase in the number of glial fibrillary acid protein (GFAP) astrocytes were observed in accordance with our study and other reports. The cerebellar cortex was susceptible to hyperglycemia-induced oxidative stress, which contributed to the neuronal damage and increased astrocyte activity (8).

Figure 10. A: Electron micrograph of the control group. The myelinated nerve fibers have intact myelin sheaths (60,000×). B–D: Electron micrographs of the diabetic group. Myelin sheaths of the nerve fibers have local or diffuse separations and breaks (12,000×, 20,000×, 25,000×). BV: blood vessels.
Immunohistochemical studies that evaluated the effects of STZ-induced diabetes on the nervous system of rats with 6 weeks or longer duration of diabetes have shown significant increases in the GFAP and S-100b constituents in diabetics compared to nondiabetic controls (1). Diabetes was shown to cause increased glial activity and the mechanism was thought to be elevated oxidative stress, whereas these histopathological and immunohistochemical changes could not be observed in STZ-induced diabetic rats after 4 weeks (1). Furthermore, degenerative light microscopic and immunohistochemical changes with GFAP, NSE, and HSP-70 were not observed in the cortex, hippocampus, or cerebellum of diabetic rats in this study. However, electron microscopic changes in the cerebellum were not studied (1).

Lechuga-Sancho et al. found no increased activation of microglia in the cerebellums of diabetic rats after a period of 8 weeks. GFAP protein levels increased 1 week after the onset of protein, followed by a decrease at 4 weeks and 8 weeks in the granular layer and white matter of the cerebellum, whereas Bergmann glial processes in the molecular layer and cerebellar vimentin levels (a marker of Bergmann glia and of reactive astrocytes) were not affected. No evidence of activation of microglia was found; however, astroglia were significantly affected. Subtypes of astroglia, such as Bergmann glia and cerebellar astrocytes, may be affected differently regarding the response to diabetes. In this study, the rise in GFAP after 1 week of diabetes was thought to reflect reactive gliosis associated with diabetes-induced cerebellar injury. In a longer period of diabetes, astroglia was observed to decrease as a result of proliferation and increased cell death (6).

In a study carried out by Fonseca et al., the effect of an 8-week diabetic status on the structure and ultrastructure of the brain was studied to show the direct neuronal damage (7). Swelling of the brain was observed...
with increased area of myelinated axons in cerebral cortex and cerebellum neuronal body. Hyperglycemia was observed to induce brain damage by causing brain acidosis and dehydration leading to ischemia. Ischemia-related edema was considered to stimulate the brain Na-K-Cl cotransporter system with edema and swelling of endothelial cells. According to these observations, endothelial and perivascular edema observed in diabetic rats were considered to induce changes in the structure of the BBB (7).

Perivascular edema, with swelling of the pericytes, astrocytes, and adipocytes disrupts the BBB. Degenerative changes in the cytoplasms of pericytes adjacent to blood vessels were also present. BBB changes in the microvessels of cerebrum and cerebellum have been observed in long-term STZ-induced diabetic subjects. We observed swelling in astrocyte elongations next to the blood vessels.

Alterations in the BBB are attributed to changes in physiochemical properties of endothelial cells and tight junctions of the cerebral microvascular structure. P-glycoprotein is localized in the apical membrane of cerebral microvascular endothelial cells. Cyclosporin A, a substrate for P-glycoprotein, was decreased in STZ-induced diabetic rats and it was associated with increased levels of P-glycoprotein mRNA in the rat brain. In a study regarding the alterations in the BBB after traumatic brain injuries in STZ-induced diabetic rats, the deterioration in BBB functions was observed to be region-specific, with the cerebellum and corpus striatum being the most susceptible region to microvascular damage (7,11).

Cell death is increased in the cerebellum with the increased levels of cleaved caspases 3, 6, and 9 and the decreased level of factor p53. Caspases 3, 6, and 9 are suggested to have a role in the increased cell turnover in the cerebellum, and increased caspase synthesis has been reported in apoptosis observed in cerebellar granule cells. Results of Lechuga-Sacho et al.’s study suggested that there is a decrease in the number of astrocytes in the cerebellum due to an increase in cell death and a decrease in proliferation. Caspase 6 is activated in diabetes after the withdrawal of trophic factors and with increased TNF-alpha levels. The trophic factor IGF-I levels are decreased and TNF-alpha levels are increased in DM. IGF-I and caspase 6 modulate caspase 3 activation. These factors are thought to have a role in apoptosis (6).

Another mechanism involved in apoptosis is related to p53, a transcription factor involved in the cell death response to a variety of signals. Reduced IGF-I levels in the cerebellum of diabetic rats is thought to lead to cell death through the activation of p53. Levels of p53 were increased in the cerebellum of diabetic rats. As a result, cerebellar alterations such as decreased astrocytic proteins, increased cell death, activation of caspases 3 and 6, increased activation of p53, and decreased cell proliferation was observed (6). We also observed puckered nuclei in Purkinje cells and extreme nuclear condensation in the cells of granular layer as a sign of apoptosis.

In a study by Antony et al., glutamate-mediated excitotoxicity in the cerebellum of insulin-induced hypoglycemic and STZ-induced diabetic rats has been reported. GLUT-3 is a brain glucose transporter located on neurons. Four groups, classified as control, diabetic, insulin-induced hypoglycemic diabetic, and insulin-induced hypoglycemic control rats, were compared. Increased gene expression in the cerebellums of the diabetic hypoglycemic group showed that cerebellar glucose transport impairment is maximal during insulin-induced hypoglycemia, leading to neuronal dysfunction (2).

Muscarnic receptor-binding assays using specific antagonists in the cerebellum showed cerebellar cholinergic receptor dysfunction due to impaired neuronal glucose transport in the cerebellum during recurrent hypoglycemia in diabetic rats (2).

Previous studies have shown that neurotransmitters such as dopamine, acetylcholine, glutamate, and GABA are altered by diabetes. A marked decrease in cAMP response element-binding protein, which has a significant role in dopamine receptor-mediated nuclear signaling and neuroplasticity in the cerebral cortex and cerebellum of diabetic rats, was observed. Phospholipase activity also decreased, leading to low levels of inositol triphosphate and in turn causing impaired release of calcium. Thus intracellular calcium decreased, resulting in cerebellar dysfunction. Dopamine receptor density decreased in the cerebellum of diabetic rats. Dopamine D1 receptor expression was downregulated in accordance with the total dopamine receptor decline. However, dopamine D2 receptor expression of cortex and cerebellum were upregulated (2,9).

A study undertaken to elucidate the quantitative synaptic changes in the dendritic spines of the Purkinje cells of rats born to STZ-induced diabetic mothers showed no ultrastructural degenerative changes in their cerebellums. However, there was an increase in the synaptic length and area of dendritic spine of their Purkinje cells, explained as the presence of a compensation in the damaged brains (12).

Studies on changes in eicosanoid synthesis in the cerebrum, cerebellum, and brain stem of diabetic rats showed changes related to abnormalities of cerebral blood flow and increased incidence of cerebrovascular disease. The effect of STZ-induced DM on rat brain prostanooid synthesis was assessed. Prostacyclin synthesis was found to be significantly reduced in DM animals in the cerebrum, cerebellum, and brain stem; however, PGF2α, PGE2, and...
TXA2 synthesis was not found to be significantly changed (13).

There are also clinical studies supporting the degenerative changes of the cerebellum in diabetes. The immunohistochemical distribution of the vitamin D-dependent calcium-binding protein (CaBP) was studied in the cerebellar vermis of noninsulin-dependent DM and nondiabetic human subjects. The volume density of CaBP-positive structure in diabetic subjects was found to be reduced (14).

A study using spectrophotometric methods in the cortex, hippocampus, corpus striatum, midbrain, thalamus, and cerebellum found that BBB permeability increased significantly in the cerebellum and corpus striatum in patients who had concurrent diabetes and trauma. The traumatic brain injury was related to disruption of the BBB, which was more severe in diabetics compared to normal subjects. The cerebellum and the corpus striatum were observed to be the most susceptible regions to trauma-induced microvascular damage in diabetics (11).

Clinically cerebellar ataxia associated with elevated levels of circulating antiglutamic acid decarboxylase antibodies in patients with type 1 DM has been reported (15–17).

Diabetes during pregnancy is shown to impair brain development in the fetus, leading to behavioral problems, motor dysfunction, and learning deficits. An experimental study on rats revealed that diabetes during pregnancy influenced the regulation of the insulin receptor and IGF-1 receptor in the developing cerebellum (18).

Clinical studies presenting cerebellar hypoplasia and agenesis in the neonatal period as a complication of neonatal diabetes are also reported in the literature (19).

A cerebellar diabetic study related to kinetic parameters of brain glutamate dehydrogenase compared the brain stem, cerebellum, and cerebral cortex of STZ-induced diabetic rats. Results pointed to the glutamate pathway as a possible regulatory function in brain neural disturbances and neuronal degeneration in diabetes as a function of age (20).

All diabetic patients are screened for known diabetes-related complications at the time of diagnosis. Diabetic neuropathy is the most evaluated neural complication. Experimental studies about neural effects of diabetes are generally focused on the cerebrum and peripheral nervous system. However, both clinical and experimental cerebellar studies are rare. The results of this study showed that diabetes affected all cerebellar layers, as well as the myelin sheath and vascular structures in the cerebellum.

The degenerative cerebellar changes observed in a short study period emphasize that further research in this area and clinical reflections should be assessed so that complications related to the cerebellum can be defined and treated at an early stage of the disease.

References


