Neurophysiologic, neuroimaging and biochemical studies in children and adolescents with Down syndrome

Neurofizjologiczne, neuroradiologiczne i biochemiczne badania u dzieci i młodzieży z zespołem Downa

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ABSTRACT

Down syndrome (DS) is one of the most common autosomal mutations. The overexpression of the β-amyloid precursor protein gene, located on chromosome 21, causes an increased production of the specific amyloid. People with DS show early Alzheimer-like dementia. We focused on some aspects involved in pathogenesis of brain accelerated degenerative processes: oxidative stress, the role of cytokines and electrophysiological and neuroimaging changes in children and adolescents with DS. Our results disclosed the disturbances of lipid peroxidation processes increased with age. We found that proinflammatory cytokines: interleukin-2, interleukin-6 and TNF-α may be involved in the pathogenesis of brain accelerated degenerative processes in DS. Quantitative analysis of the REM sleep from DS group disclosed reduction of the power mainly in the alpha when comparing the healthy group. In our other study, we examined a cohort of patients with DS evaluated over a 13-year period at our Department. Incidence of epilepsy in children with DS was higher than in the general population. Good control of seizures was obtained in 40% of children with DS. Quantitative analysis of EEG revealed a "poor" background brain activity in patients with DS and epilepsy. In the MRI study, we demonstrated a significantly smaller total brain volume, significantly smaller frontal and temporal lobes volumes including significantly smaller hippocampus and amygdala volumes. 1HMRS examinations disclosed the abnormal metabolism of stimulatory amino acids in children with DS.

Key words: Down syndrome, oxidative stress, cytokines, EEG, MRI

Human trisomy 21 (Down syndrome) results from the presence of 3 copies of chromosome 21 instead of 2 and it is the most frequent chromosomal abnormality affecting approximately 1 in 800 live births. The extra chromosome adversely affects many phenotypic and physiological factors. DS is characterized by mental retardation, immunodeficiency, cataracts, increased incidence of leukemia, signs of premature aging, and neuropathological alterations similar to those found in AD [1].

The neuropathological hallmark lesions (tangles and plaques) of Alzheimer’s disease (AD) are present in the brains of all adults with DS by the age of 40, which suggests a shared genetic susceptibility to DS and AD. However, these characteristic tangles and plaques do not necessarily mean that all individuals with DS will develop AD. The prevalence of AD in people with DS increases significantly with age. However, the nature of the early clinical presentation, course, and incidence rates of dementia are uncertain.
Despite the nearly universal occurrence of AD pathology by the age of 40, there is a wide variation in the age of onset of clinical dementia. Most studies have indicated that the average age at onset of dementia is between 50 and 55 years of age, with a range from 38–70 years [2,3]. Many studies have confirmed that age-related cognitive decline and dementia affecting people with DS occurs 30–40 years earlier than in the general population. Age-specific rates of dementia begin to increase in the patient’s 30s from 1-2% to 40% in the 50s [2,3], hence dementia is becoming an increasingly important issue in people with DS as life expectancy continues to increase.

Despite the fact that AD and DS are distinct disorders, the neuropathology is similar in AD and in adults with DS. The pathophysiological changes in neurons have been the subjects of many investigations [4,5].

There is evidence for a common genetic and pathophysiological background of dementia in DS and AD. One of the early-onset AD genes is found in chromosome 21. Single base mutation in the amyloid precursor protein (APP) gene in chromosome 21 leads to accumulation of amyloid protein in senile cells. A similar mechanism of “precocious aging” of the brain has been observed in DS [6].

The neuropathological manifestations of AD in DS have been at least in part attributed to triplication and overexpression of the gene for amyloid precursor protein (APP) located on chromosome 21 [7]. In fact, an additional copy of APP can cause early onset AD with cerebral amyloid angiopathy, even when only small regions of chromosome 21 including only the APP gene are triplicated. Triplication of chromosome 21 leads to an increase in expression levels of its genes. APP is expressed at levels which are four- to fivefold higher in DS than in the general population. This is not only due to triplication of the gene, but is also caused by regulators of APP expression, for example ETS2, present on chromosome 21, which have increased expression levels [8]. Processing of APP can result in the production of betaamyloid (Aβ) which is deposited extracellularly as a core disease feature in the brains of people with AD.

There is increasing evidence supporting the association between lipid peroxides/free radicals and the development of DS in early childhood. Oxidative stress is defined as an imbalance between production of oxygen-derived free radicals and their removal by antioxidants. The activity of superoxide dismutase (SOD) a key enzyme in the metabolism of oxygen-derived free radicals is increased in DS [9]. This increase in SOD activity may alter the normal steady state equilibrium of reactive oxygen species leading to oxidative injury in DS. In this chain of factors oxygen free radicals and antioxidant systems play an important role in DS.

SOD catalyses the dismutation of superoxide radicals to hydrogen peroxide which is further metabolised to water by glutathione peroxidase (GPx) or catalase (CAT). The known reactive oxygen radical can, for example, readily initiate lipid peroxidation resulting in damage to cell membranes. Because the brain is rich in highly polyunsaturated fatty acids which are particularly susceptible to lipid peroxidation, it is potentially vulnerable to this type of damage. It is hypothesised that an over-expression of SOD causes free radical mediated damage and that this may contribute to the learning disability and early onset of AD which are typical of DS. Oxygen-derived free radicals play an important role in the pathogenesis of many pediatric diseases, including retinopathy of prematurity, neonatal intraventricular haemorrhage, reperfusion injury, DS, mitochondrial encephalopathies, epilepsy and schizophrenia [10-14]. Excess production of free radicals during ischaemia or impaired antioxidant mechanisms may cause oxidative stress which may induce a number of pathophysiological processes and result in cell injury [10,12]. Superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), hydrogen peroxidase and catalase (CAT) are the antioxidant enzymes which block the initiation of free radical chain reactions [15]. Impaired antioxidant defense mechanisms can result in cell membrane damage, alterations in membrane fluidity and permeability, and oxidative changes in proteins. Role of free oxygen radicals in asphyxiated neonates was studied [16].

Based on clinical history, an allergic mechanism and the involvement of the immune system have also been hypothesized to be involved in DS precipitation. The immune function in individuals with DS has been shown to be defective [17]. Dysregulation of the immune system is one characteristic pathological feature of the syndrome, and leads to increased susceptibility to viral or bacterial infections and leukemia. These observations, together with the demonstration of a frequent occurrence of HBsAg carrier state and of autoantibodies, have prompted investigations of the immune function in DS patients [17].

Thymic morphological and functional abnormalities have been also demonstrated [17].

The trisomic chromosome 21 carries genes for receptors and ligands of the interferon family. In DS patients, abnormalities in thymus anatomy depend on interferon-γ (IF-γ) and tumour necrosis factor-α (TNF-α) overexpression was found [18]. Interferon-γ can also cause neurodegeneration and β-amyloid production in DS and in its animal model, the trisomy 16 mouse [18], and accounts for cognitive impairment. Apolipoprotein E (ApoE) is a polymorphic protein that plays a central role in plasma lipoprotein metabolism. Its production and accumulation are increased in central nervous system disorders like a AD and in DS [19]. DS is associated with high frequency of celiac disease, a chronic inflammatory disease of the small intestinal mucosa. In the literature there are only few studies on pro- and anti-inflammatory interleukins in subjects with DS [17, 20]. Studies on cytokines in DS patients have shown fluctuations of cytokine levels but conflicting results have been reported on the mechanisms involved.

Many authors have analyzed the importance of the relationship between REM sleep and learning or memory [21-23]. On the other hand, a quantitative EEG (power spectra and coherence) provides objective measures in the search for global or focal abnormality which, if present, may signal an underlying organic or non-organic processes [24,25]. Petit et al. [26] showed that EEG slowing
during REM sleep is a more sensitive biological marker of Alzheimer’s disease than is EEG slowing during wakefulness. The REM sleep EEG measure allowed complete discrimination of AD patients at mild to moderate stages from age-matched control subjects. Although quantitative analysis of EEG background activity has been frequently done [27,28], the studies that dealt with this particular aspect on EEGs were rare in children with DS. Most previous studies [29-31] on EEG in patients with DS were conducted in adult patients or at school age. However, one theoretical possibility is that quantitative analysis of the background activity could disclose subtle abnormalities not detected by visual analysis.

The seizures and epilepsy were not mentioned in the original description of DS [32]. The prevalence of epilepsy in children with DS is now known to be higher than in the general population but lower than in patients with mental retardation [32]. It is reported that the rates of epilepsy in DS range from 1% to 13% [32,33]. The increased seizure susceptibility in DS has been attributed to inherent structural anomalies of the brain or to associated medical complications, such as cardiovascular abnormalities and recurrent infections [34].

Magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (1HMRS) provide new possibilities for the evaluation of brain “precocious aging” in DS. 1HMRS allows non-invasive in vivo determination of brain metabolite content, or rather of the proportions of the metabolites in the respective structures of the brain. Spectroscopy facilitates assessment of such metabolites as N-acetylaspartate (NAA), choline (Cho), creatinine (Cr), myoinositol (mI) and gamma-aminobutyric acid (GABA), which are known to play a key role in the function of the nervous system, e.g. in the processes of memory and learning. 1HMRS is used in the diagnosis of metabolic disorders of the central nervous system, ischemic-hypoxic conditions, brain tumors and AD [35,36]. Spectroscopy is also applied for DS diagnostics in association with brain “precocious aging” processes and symptoms of dementia of the Alzheimer type [37]. The literature regarding this subject is sparse and refers mainly to DS in adults. Authors have measured neurotransmitters in the hippocampal region, in the basal nuclei, and in the parietal and occipital lobes [36,37]. Only Berry et al. [38] have shown a significant increase in myoinositol level in the basal ganglia (striatum) in DS children compared to the control group.

From the clinical point of view, great expectations are associated with neuroradiologic methods, which are hoped to make it possible to find the markers of dementia progression in subjects at risk of the development of AD in DS and to find the markers of specific cognitive and developmental deficits seen in individuals with DS [39,40]. Early neuropathological signs of AD are evident predominantly in the temporal cortex [41]. Because children with DS are at increased risk for dementia thought to be of the Alzheimer’s type, structural or metabolic brain changes in DS, especially in the temporal lobes and/or frontal lobes, may predict the onset of dementia.

Previous neuroimaging studies of adults with DS report volume reduction of the hippocampus and amygdala [42,43] and temporal lobes and/or frontal lobes [44,45].

Little is known about the hippocampus and amygdala volume in children with DS. Pinter et al., 2001 [46] indicate that hippocampal volumes are decreased out of proportion to overall brain volumes in children and young adults with DS, whereas adjusted amygdala volumes do not differ significantly from controls. Considering the high prevalence of DS, surprisingly few MRI studies of affected children have been published. Jernigan et al. [47] reported smaller overall brain volumes, with disproportionately smaller volumes in frontal, temporal, and cerebellar regions, in a volumetric MRI study of children with DS. As in the adult studies, volumes of thalamus and lenticular nuclei were noted to be normal.

Most studies had been performed in adult patients with DS. So, we focused on some aspects involved in the pathogenesis of premature aging of the brain in children with DS: oxidative stress, the role of cytokines and electrophysiological and neuroradiological changes in children and adolescents with DS. Elucidation of the mechanisms responsible for “precocious aging” of the brain in DS may create new possibilities for more effective treatment of this disease.

OXIDATIVE STRESS IN DS

We found some disturbances of lipid peroxidation in children with DS [48]. The present study included 41 children with DS (12 females and 29 males) between 1 and 17 years of age, mean age 8.57±6.19. A group of 61 healthy children and adolescents (32 females and 29 males) between 4 and 17 years of age, mean age 10.11±5.85 included in the study were recruited as a comparison group. The study objective was to assess the processes of lipid peroxidation with malondialdehyde (MDA) as its major indicator as well as the activities of antioxidative enzymes: superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and glutathione reductase (GR) in the serum of children with DS.

We found a significant increase of GPx activity in serum of children with DS compared to controls (p=0.016). The present data demonstrated that SOD, and GR in serum were not significantly different between DS patients relative to match normal control subjects. No difference in MDA concentration in serum between the DS and the control group was found. Our findings are partially in an agreement to those reported by Kedziora et al., 1990; Jovanovic et al., 1998; Durackova et al., 1999 [9,49,50] whose assayed the lipid peroxidation and antioxidant enzymes in DS children. They found the significant increase in MDA levels in serum and the activities antioxidant enzymes of patients were compared with the control group. In conclusion our results suggest that increased serum GPx activity could be a suitable protection mechanism against peroxidation processes of DS patients.

In our next paper MDA concentration and activities of SOD, GPx and GR were determined in the erythrocytes in children and adults with DS [51]. The study group con-
sisted of 24 children with DS, aged 8 months - 17 years, mean age 8.9± 5.0. The control group included 24 healthy children, aged 1.5 - 17 years (mean age 10.93±5.0). The second study group consisted of 42 adults with DS, aged 21 - 53 years (mean age 34.69 ± 8.54). The control group included 35 healthy adults, aged 23 - 65 years (mean age 40.54 ± 12.0). In the DS group, the MDA levels in erythrocytes were statistically significantly higher than in the control subjects (p<0.001). It was found a significant increase of SOD (p<0.001), GPx (p=0.003) and GR (p<0.001) activity in the erythrocytes of DS group compared to controls.

In people with DS was found a higher concentration of MDA in erythrocytes. It’s the rate of increased oxidation of lipid membranes. SOD, GPx, GR activity in the erythrocytes in DS patients was higher compared with controls. Activities of the antioxidative enzymes decreased with age, which suggests “exhaustion of the enzymes”.

Our results confirmed the disturbances of lipid per-oxidation processes in DS and suggest the activation of antioxidative mechanisms [48,51]. Its important indicator seems to be the increase of SOD, GPx and GR activity in erythrocytes and GPx activity in serum of the DS patients and its increased with age. The other important indicator was the increase of MDA concentration in erythrocytes with age.

CYTOKINE FLUCTUATIONS IN DS

Cytokines are small proteins produced by most cells in the body; they perform multiple biologic activities that promote cell-cell interaction. In order to understand the role of cytokines in DS, in our study we focused on selected anti-inflammatory cytokines [52].

We analyzed interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13) levels in plasma from children with DS. The study involved 53 children and adolescents, including 20 with DS (mean age 8.57±6.19 years; range 5-17). We recruited thirty three healthy subjects as controls. The healthy children were 8-17 years of age (mean age 12.11±3.46). IL-4 was detected in 25% subjects with DS and in 28.6% healthy subjects. IL-13 was detected in 15% patients with DS and in 15.2% healthy subjects. IL-10 was detected in one subject with DS only and in two healthy children.

We did not find any significant differences or trends between both studied groups. No significant correlations between measurable cytokine levels and age or gender were found [52]. However, immune dysfunction in children with DS could not be excluded.

In our next study, we focused on selected pro-inflammatory cytokines in DS [unpublished data]. We analyzed interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-1α (IL-1α), soluble receptor for tumor necrosis factor (STNFR1) and tumor necrosis factor alpha (TNF-α) levels in plasma from children with DS compared to healthy children. The study involved 44 children and adolescents with DS (mean age 10.45± 3.2 years). We recruited 24 healthy children as controls (mean age 11.27± 4.0 years). The IL-2 (p=0.0002), IL-6 (p<0.001) and TNF-α (p=0.0029) levels were significantly higher in DS in comparison with levels in the control group. We did not find any significant differences in the STNFR1 and IL-1α levels.

Our results suggest that pro-inflammatory cytokines: TNF-α, IL-2 and IL-6 may be involved in the pathogenesis of DS.

CELL IMMUNITY DYSFUNCTION IN DS

DS is the most frequent chromosomal anomaly associated with long lasting infections caused by the defect of original immune system. Up to date investigations on immunological conditions did not show any coherent results. The aim of our study was the assessment of cell immunity in children with DS using CD3+, CD4+ and CD8+ lymphocyte T ratio in peripheral blood in comparison to reference group [53]. The study was carried out on 28 children total (17 boys and 11 girls) with DS within the age of 6 to 12. Reference group consisted of 26 children (16 boys and 10 girls) in the same age range. There were no signs of infections in investigated groups, children did not take any drugs. Lymphocyte T subpopulation were determined by flow cytometry method. In the children with DS in comparison to reference group there was statistically higher percentages of T lymphocyte CD3+ (69.0 vs. 64.85%, p < 0.04) and CD8+ (CD8+ 36.29, vs. 26.46%, p<0.01) in peripheral blood reported. The ratio of T lymphocyte with CD4+ receptor expression in the group with DS did not present any statistical differences. Significantly lower value of Th/Ts ratio was reported in the group of DS children than in the reference group. The present results suggest cell immunity dysfunction in DS children.

THE ELECTROPHYSIOLOGY OF DS

Many authors have analyzed the importance of the relationship between REM sleep and learning or memory [21-23]. On the other hand a quantitative EEG (power spectra and coherence) provides objective measures in the search for global or focal abnormality which, if present, may signal an underlying organic or non-organic processes [24,25]. Petit et al. [26] showed that EEG slowing during REM sleep is a more sensitive biological marker of Alzheimer’s disease than is EEG slowing during wakefulness. The REM sleep EEG measure allowed complete discrimination of AD patients at mild to moderate stages from age-matched control subjects. Twenty-one patients aged 1-8 years with genetically confirmed DS were included in this study [54]. Patients did not take any pharmacological agents which could exert effects on sleep or EEG. Patients with seizures or epilepsy were excluded from the study. The control group included twenty-one healthy subjects, matched for chronological age and gender. EEG recordings were performed while the patients were in a REM sleep during the first 40 minutes. Visual analysis of the background activity showed no abnormalities in the EEGs from all the subjects of the control children. In children with DS sleep REM was less pronounced as compared to controls. Quantitative analysis of the sleep REM from DS group disclosed reduction of the power mainly in the alpha when comparing the healthy group. Moreover, beta, theta and delta bands did not differ significantly between the groups. In the spectral analysis, we
detected significant (p<0.001) decrease of alpha bands at the occipital derivations [34]. The EEG may be an important tool in the clinical diagnosis of Alzheimer-type dementia in patients with DS.

Although seizures and epilepsy were not mentioned in the original description of DS [32], the prevalence of epilepsy in children with Down syndrome is now known to be higher than in the general population but lower than in patients with mental retardation [32]. It is reported that the rates of epilepsy in Down syndrome range from 1% to 13% [32,33]. In this study, we examined the prevalence of epilepsy, seizure types, and electroencephalography (EEG) records, and drug therapy in a cohort of patients with DS evaluated over a 13-year period at our Department of Pediatric Neurology in Białystok, Poland [55]. The medical records of children and adolescents with DS who were treated at the Department of Pediatric Neurology of Medical University in Białystok between 1994 and 2007 were reviewed for history of seizures and epilepsy. Data on seizure type, age of onset, drug treatment, seizure control, and possible etiology was analyzed. Seizure classification was based on clinical reports and EEG results. A group of 10 children with DS without epilepsy matched for age and gender was recruited as controls. The second group was 28 children with epilepsy without DS matched for age and gender included as an additional comparison group. Of the 252 patients (97 girls and 155 boys) aged 1–20 years with genetically confirmed DS, 15 (6%), 10 boys and 5 girls, had epilepsy and it is higher than in the general population. No relationship was found between seizure type, age at seizure onset and presence or absence of a known etiology. Good control of seizures was obtained in 40% of children with DS, it shows a poor prognosis of epilepsy in this syndrome. EEG was performed on all patients with DS. The EEG was found to be abnormal in DS with epilepsy in 100%.

In this report, we have noted significant increase in power at theta, delta, and beta and decrease in alpha in DS compared with non-DS with epilepsy [55].

MAGNETIC RESONANCE SPECTROSCOPY (1HMRS)

Magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (1HMRS) provide new possibilities for the evaluation of brain "premature aging" in DS.

The literature regarding this subject is sparse and refers mainly to DS in adults. Taking this into consideration, we attempted to assess the metabolic profile in the frontal and temporal lobes of DS children [56,57]. The study group consisted of thirty-four children, including 14 with DS (aged 6-17, mean 10.92±3.49) and 20 healthy children (aged 6-15, mean 10.9±2.44 years). In all cases, 1HMRS investigations were performed to assess the metabolic profile of NAA, Cho, Glx and GABA. The frontal lobes with reference to the internal marker Cr. The ratios were decreased in the temporal lobes of DS children compared to the control children. The differences relating to NAA/Cr (p=0.0044), Cho/Cr (p=0.013), ml/Cr (p=0.026) and GABA/Cr (p=0.017) were statistically significant. A significantly positive correlation was found between NAA/Cr and age in healthy children (r = 0.6039, p = 0.00480) but not in the DS group (r = 0.2684, p = 0.2525). A significantly positive correlation was found between Cho/Cr and age in the DS group (r = 0.2684, p = 0.0286) and in the control group (r = 0.5344, p = 0.0152). The level of significance was higher in the control group. A positive correlation was observed between ml/Cr and age in the DS group (r = 0.04147, p = 0.0690), whereas a negative correlation was noted in the control group (r = –0.0859, p = 0.07189).

Based on the literature data [37,38] and our findings, it can be assumed that, in DS patients, the destructive processes predominate over the repair events. Our findings indicate that neurotransmission disorders in the CNS of patients with trisomy 21 may be responsible for the impaired memory, learning and accelerated brain aging in DS subjects.

A VOLUMETRIC MRI STUDY

In this study we presented quantitative MRI measurements of the frontal and temporal, hippocampus, amygdala and total brain volume in children with DS in relation to clinical status [58]. MRI of 49 patients was reviewed prospectively. Volumes of the brain structures were blind measured by the radiologist. The study included 23 children with DS (aged 3-15 years, mean 6.7 ± 3.72) and 26 healthy children (aged 4-15 years, mean 8.3 ± 2.44). A group of 26 healthy right-handed children matched for age and gender were recruited as a comparison group.

The DS group had a significantly smaller right and left temporal (TR and TL) and frontal (FR and FL) lobes volume than the control group (TR- 63.167cm3±9.535 vs 77.6cm3±12.067; p= 0.001; TL- 61.472cm3±9.535 vs 71.624cm3±10.59; p =0.005; FR-188.28cm3±32.8 vs 247.528cm3±23.45; p<0.001; FL-182.059cm3±31.305 vs 243.302cm3±21.364; p<0.001). The mean difference was approximately 18.6% and 14.2% for TR and TL and 24% and 25.2% for FR and FL. DS group had a significantly smaller right (HP-R) and left (HP-L) hippocampus volume than the control group did (HP-R 1.922mm3±0.303 vs 1.953mm3±0.316; p< 0.001; HP-L 1.110mm3±0.278 vs 1.989mm3±0.211; p< 0.003). The mean difference was approximately 39%. The DS group also had a significantly smaller right (AR) and left (AL) amygdala volume than did the control group (AR-0.559cm3±0.145 vs 0.731cm3±0.147;
p = 0.003; AL 0.522cm³±0.142 vs 0.741cm³±0.177; p = 0.003). The mean difference was approximately 23.5%. The total brain volume measurement was significantly smaller for the children with DS compared with controls (932.52cm³±124.18 vs 1074.37cm³±89.15; p = 0.006). The mean difference was approximately 13.3%. A positive correlation was found between right and left hippocampus volume and age in the DS group (HP-R r = 0.452491 p = 0.030162; HP-L r = -0.436974 p = 0.037076). A negative correlation (r = -0.441113 p = 0.03) between right hippocampus volume and mental development in children with DS was noted. No significant relationship between a left hippocampus (r = -0.215641 p = 0.323056), right and left amygdala volume (AR r = -0.30104 p = 0.891543; AL r = -0.132088 p = 0.547982), total brain volume (r = -0.058364 p = 0.791378) and mental development in children with DS was noted.

Our results have confirm the results of previous studies with respect to overall patterns of brain volumes in children with DS. The strengths of our study include our relatively large group size and its wide age range, which also included children under age five. The limitations of our report include not tested cerebellum, parietal and occipital lobes, and sub-cortical structures in children with DS. Further studies are needed to investigate cerebellum, the parietal and occipital lobes, and volumes of sub-cortical brain structures.

CONCLUSIONS

1. Our results disclosed the disturbances of lipid peroxidation processes in patients with DS increased with age.
2. The pro-inflammatory cytokines: interleukin-2, interleukin-6 and TNF-α may be involved in the pathogenesis of accelerated degenerative processes in DS.
3. No significant fluctuations of selected anti-inflammatory cytokines in children with DS have been found. However, immune dysfunction in children with DS could not be excluded.
4. The present results suggest the cell immunity dysfunction in DS children.
5. Quantitative analysis of the sleep REM from DS group disclosed the reduction of the power, mainly in the alpha.
6. Quantitative analysis of EEG revealed a poor background brain activity in patients with DS and epilepsy compared with the control group.
7. 1H MRS examinations seem to confirm the abnormal metabolism of stimulatory amino acids in children with DS.
8. The quantitative MRI measurements of brain structures in DS demonstrated a significantly smaller total brain volume, significantly smaller frontal and temporal lobes volumes including significantly smaller hippocampus and amygdale volumes.

REFERENCES

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