ORIGINAL PAPER/*ARTYKUŁ ORYGINALNY*

A volumetric magnetic resonance imaging study of brain structures in children with Down syndrome

Wolumetryczne badania struktur mózgowia metodą rezonansu magnetycznego u dzieci z zespołem Downa

Joanna Śmigielska-Kuzia[1], Leszek Boćkowski[1], Wojciech Sobaniec[1], Krzysztof Sendrowski[1], Beata Olchowik[1], Magdalena Cholewa[1], Adam Łukasiewicz[2], Urszula Łebkowska[1]

[1]Klinika Neurologii i Rehabilitacji Dziecięcej, Uniwersytet Medyczny w Białymstoku
[2]Zakład Radiologii, Uniwersytet Medyczny w Białymstoku

Neurologia i Neurochirurgia Polska 2011; 45, 4: 363–369

Abstract

Background and purpose: Down syndrome (DS) is the most common genetic cause of mental retardation with deficits in language and memory. Mental retardation of varying degrees is the most consistent feature of DS. The objective of this study was to use high-resolution magnetic resonance imaging (MRI) techniques to investigate the volumes of the hippocampus, amygdala, and temporal and frontal lobes in children with DS compared with healthy children.
Material and methods: MRI of 49 patients was reviewed prospectively. The study included 23 children with DS (9 girls and 14 boys, mean age 6.7 ± 3.7 years) and 26 healthy children (11 girls and 15 boys, mean age 8.3 ± 2.4 years). Volumes of the right and left hippocampus, the right and left amygdala, temporal and frontal lobes and the total brain volume were measured by a radiologist who was unaware of the diagnosis.
Results: Total brain volume in children with DS was significantly lower compared with controls. It was associated with significantly lower volume of the frontal and temporal lobes. Children with DS had a significantly smaller right and left hippocampus volume and a significantly smaller right and left amygdala volume than did the control group. We also found a negative correlation between mental retardation and volume of the right hippocampus.

Streszczenie

Wstęp i cel pracy: Zespół Downa (ZD) jest najczęstszą genetyczną przyczyną upośledzenia umysłowego, deficytów mowy i pamięci. Upośledzenie umysłowe różnego stopnia to najbardziej stała cecha zespołu Downa. Celem pracy było wykorzystanie techniki badania rezonansu magnetycznego (RM) wysokiej rozdzielczości do porównania objętości hipokampów, ciał migdałowatych, płatów skroniowych i czołowych dzieci z ZD w porównaniu z dziećmi zdrowymi.
Materiał i metody: Ocenie poddano 49 badań RM. Badaniem objęto 23 dzieci z ZD (9 dziewczynek i 14 chłopców, średnia wieku: 6,7 ± 3,7 roku). Grupę kontrolną stanowiło 26 dzieci zdrowych (11 dziewczynek i 15 chłopców, średnia wieku: 8,3 ± 2,4 roku). Objętość prawego i lewego hipokampa, prawego i lewego ciała migdałowatego, płatów skroniowych i czołowych oraz całkowita objętość mózgu były mierzone manualnie przez radiologa nieznającego rozpoznania.
Wyniki: Całkowita objętość mózgu w grupie dzieci z ZD była istotnie mniejsza w porównaniu z grupą kontrolną. Wiązało się to z istotnie mniejszą objętością płatów czołowych i skroniowych. Grupa dzieci z ZD miała istotnie mniejszą objętość prawego i lewego hipokampa oraz prawego i lewego ciała migdałowatego w porównaniu z dziećmi zdrowymi. Wykazano

Correspondence address: dr Joanna Śmigielska-Kuzia, Klinika Neurologii i Rehabilitacji Dziecięcej UMB, ul. Waszyngtona 17, 15-274 Białystok, e-mail: jsmig1@poczta.onet.pl
Received: 30.08.2010; accepted: 26.02.2011

Conclusions: The presence of these abnormalities from an early age contributes to the specific cognitive and developmental deficits seen in children with DS.

Key words: hippocampus, amygdala, MRI, volume, Down syndrome.

jednocześnie ujemną korelację pomiędzy stopniem upośledzenia umysłowego a objętością prawego hipokampa.
Wnioski: Obecność opisanych zaburzeń od najmłodszych lat przyczynia się do konkretnych deficytów poznawczych i rozwojowych u dzieci z ZD.

Słowa kluczowe: hipokamp, ciało migdałowate, rezonans magnetyczny, objętość, zespół Downa.

Introduction

Down syndrome (DS), the most common genetic cause of mental retardation, results in characteristic physical and neuropsychological findings, including mental retardation and deficits in language and memory [1-4]. Mental retardation of varying degrees is the most consistent feature of DS [5]. Numerous studies on cognitive development in DS have been performed, yielding a profile of global delays with disproportionately impaired speech and language [2-4]. Some studies also have identified major deficits in both short-term and long-term verbal memory [6-8].

The amygdala and hippocampal complex, two medial temporal lobe structures, are linked to two independent memory systems, each with unique characteristic functions. The hippocampal formation is a malleable brain structure that is important for certain types of learning and memory and for converting short-term memory to more permanent memory. The amygdala is a complex neural structure implicated in several aspects of emotional and social behaviour. The amygdala is a structure that plays a critical role in fear learning and is also an important target of anxiety and stress. The hippocampus and amygdala are regions known to be severely affected by the characteristic neuropathology of Alzheimer disease (AD) [9-11]. From the clinical point of view, great expectations are associated with neuroradiological 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 [12-15]. Early neuropathological signs of AD are evident predominantly in the temporal cortex [16-19]. Because children with DS are at increased risk for dementia thought to be of the Alzheimer 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 [2, 5-9] and temporal lobes and/or frontal lobes [16-18].

Little is known about the hippocampus and amygdala volume in children with DS. Pinter *et al.* [20] indicated that hippocampal volumes were decreased out of proportion to overall brain volumes in children and young adults with DS, whereas adjusted amygdala volumes did not differ significantly from controls. Considering the high prevalence of DS, surprisingly few MRI studies of affected children have been published. Jernigan *et al.* [21] reported smaller overall brain volumes, with disproportionately smaller volumes in frontal, temporal, and cerebellar regions, in a volumetric MRI study of six children with DS. As in the adult studies, volumes of thalamus and lenticular nuclei were normal.

The results of our previous studies indicate brain metabolic neurotransmitter changes in the frontal and temporal lobes of the central nervous system in children with DS [22,23]. Here, we present quantitative MRI measurements of the frontal and temporal lobes, hippocampus, amygdala and total brain volume in children with DS compared with healthy children.

Material and methods

The study included 23 children with DS (9 girls and 14 boys, aged 3-15 years, mean 6.7 $\pm$ 3.7) and 26 healthy children (11 girls and 15 boys, aged 4-15 years, mean 8.3 $\pm$ 2.4). A group of 26 healthy right-handed children matched for age and gender were recruited as a comparison group. All subjects were free from neurological or psychiatric diseases, had normal intellectual development, and their brain MRI scans were normal. They were all patients of the Department of Paediatric Neurology and Rehabilitation, Medical University of Bialystok and its Outpatient Clinic. Mental development was divided into small delay, 70 to 84 IQ (one child with DS); moderate delay, 50 to 69 IQ (16 patients with DS); and severe delay, $<$ 50 IQ (six children with DS). Normal children have an IQ $>$ 90.

None of the children with DS and all healthy subjects had normal intelligence.

The study was approved by the Ethical Committee at the Medical University of Bialystok, Poland. Informed consent was obtained from the participants' parents.

The MRIs were acquired using an Eclipse 1.5 T scanner (Marconi Medical Systems,. Cleveland, OH, USA) at the Radiology Department in the Medical University of Bialystok. After a scout sequence was obtained to ensure symmetric position of the subject's head, a standard imaging protocol was used – transverse, sagittal and coronal T1-weighted (300/4.5 ms [TR/TE]) and T2-weighted (5000/127.6 ms) sequences with 5-mm-thick sections and no gap were acquired. Volumes of the right and left hippocampus, the right and left amygdala, temporal and frontal lobes and the total brain volume were measured by a radiologist who was unaware of the diagnosis. Images were imported to the Vitrea workstation (Vital Images, USA) for semiautomated image processing analysis and quantification. Outlines of the amygdala and hippocampus were established using multiple sources, including neuroanatomical atlases, and measured according to the method described by Soininen *et al.* [24]. Hippocampal volume included the volumes of the dentate gyrus, hippocampus proper, and the subicular complex. The amygdaloid volume consisted of the volumes of the deep nuclei of the amygdala, the superficial nuclei of the amygdala and the remaining nuclei of the amygdala. The hippocampal and amygdaloid volumes, as well as lobes and total brain volumes, were measured by the same observer. The boundaries of the hippocampus and amygdala were manually outlined by a trackball-driven cursor on coronal MR images for each side (Fig. 1) from anterior to posterior. Volume was measured semi-automatically by adding together all sub-volumes.

The total intracranial volume was obtained on sagittal sections, and the volumes of the hippocampal formation and the amygdala were standardized according to the method used by Lehericy and colleagues [25]; that is, the volume of the hippocampal formation was divided by the total brain volume.

Statistical analyses were performed using Statistica 6.0 software. Descriptive analysis and matched *t*-tests were used as appropriate. Spearman analysis was used to measure the dependence between mental development and age of DS children and controls. The level of significance for all tests was set at < 0.05.

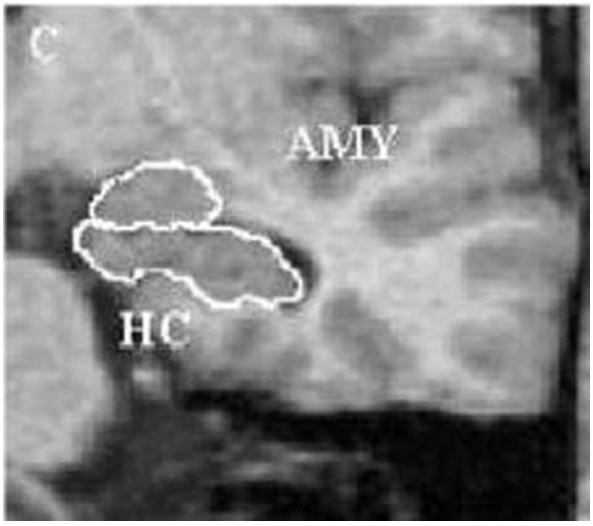

Fig. 1. Manually traced boundaries of the amygdala (AMY) and the hippocampus (HC) on coronal magnetic resonance images in patient with Down syndrome

Results

The volumes of studied brain structures in the DS group and controls are provided in Table 1. The DS group had a significantly smaller right and left temporal and frontal lobe volume than the control group. The mean difference was approximately 18.6% and 14.2% for the right temporal lobe and left temporal lobe and 24% and 25.2% for the right frontal lobe and left frontal lobe.

The DS group had a significantly smaller right and left hippocampus volume than the control group. The mean difference was approximately 39%. The DS group also had a significantly smaller right and left amygdala volume than did the control group. The mean difference was approximately 23.5%. The total brain volume measurement was significantly smaller for the children with DS compared with controls. The mean difference was approximately 13.3%.

A positive correlation was found between right and left hippocampus volume and age in the DS group (Table 2 and Fig. 2). A negative correlation between right hippocampus volume and mental development in children with DS was noted. No significant relationship between left hippocampus, right and left amygdala volume or total brain volume and mental development in children with DS was noted (Table 3 and Fig. 3).

Discussion

In this study, we used advanced MR techniques to document in vivo impaired cerebral development, pre-

Table 1. Volumes of specified structures of the brain in children with Down syndrome ($n = 23$) versus controls ($n = 26$)

Structure	Volume (cm³); mean ± SD (range)		*P*-value
	Children with Down syndrome	Control group	
Total brain	932.52 ± 124.18 (756.76-1098.97)	1074.37 ± 89.15 (950.79-1286.16)	0.006
Right amygdala	0.559 ± 0.145 (0.375-0.987)	0.731 ± 0.147 (0.546-0.956)	0.003
Left amygdala	0.522 ± 0.142 (0.3477-1.007)	0.741 ± 0.177 (0.5099-1.069)	0.003
Right hippocampus	1.192 ± 0.303 (0.591-1.552)	1.953 ± 0.316 (1.562-2.522)	< 0.001
Left hippocampus	1.110 ± 0.278 (0.616-1.616)	1.989 ± 0.211 (1.463-2.324)	0.003
Right temporal lobe	63.167 ± 9.535 (44.48-77.13)	77.6 ± 12.067 (59.08-107.7)	0.001
Left temporal lobe	61.472 ± 9.535 (46.67-79.95)	71.624 ± 10.59 (59.95-99.5)	0.005
Right frontal lobe	188.28 ± 32.8 (142.5-245.02)	247.528 ± 23.45 (205.28-303.25)	< 0.001
Left frontal lobe	182.059 ± 31.305 (121.63-242.76)	243.302 ± 21.364 (193.08-295.33)	< 0.001

SD – standard deviation

Table 2. Correlation between the volume of specified structures of the brain and age of children with Down syndrome (r – Spearman rank correlation coefficient)

Structure	*r*	*t*-value	*p*-value
Total brain volume	0.220	1.035	0.313
Right amygdala	0.233	1.097	0.285
Left amygdala	0.235	1.107	0.281
Right hippocampus	0.452	2.325	0.030
Left hippocampus	0.437	2.226	0.037
Right temporal lobe	0.209	0.978	0.339
Left temporal lobe	0.173	0.803	0.430
Right frontal lobe	0.073	0.336	0.740
Left frontal lobe	0.1701	0.791	0.438

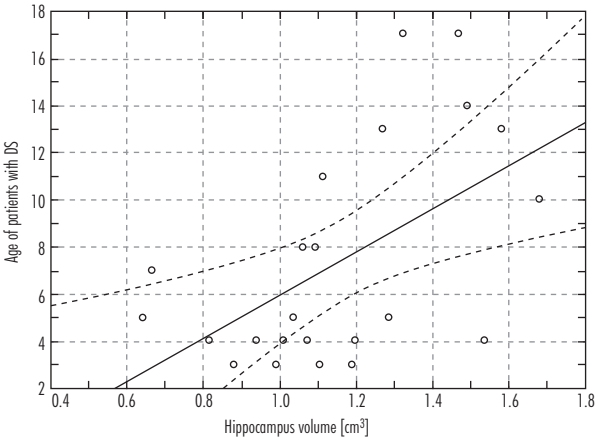

Fig. 2. Correlation between left and right hippocampus volume and age of patients with Down syndrome ($r = 0.504$, $p = 0.014$)

sented by children with DS. The impairments in cerebral development included significant reductions in the frontal and temporal lobe, hippocampal and amygdala volumes in comparison to controls. The total brain volume was significantly smaller for the children with DS compared with controls. We also found a positive correlation between the right and left hippocampus volume and age in the DS group. A negative correlation between right hippocampus volume and mental development in children with DS was noted. No significant relationship between the left hippocampus, right and left amygdala volume, total brain volume and mental development in children with DS was noted.

Our findings are in accordance with previous neuroimaging studies in adults with DS [14-19]. Our results are consistent with a recent study of Aylward *et al.* [26], who reported decreased hippocampal volume and no significant differences in amygdala volumes among nondemented adults with DS. They found that hippocampal volumes are disproportionately small in individuals with DS, even before any signs of cognitive impairment occur. In non-demented individuals with DS, hippocampal volumes did not decrease with age, as indicated by the lack of a significant correlation between age and hippocampal volume. Amygdala volumes of the demented DS subjects were significantly smaller than

Table 3. Correlation between the volume of specified structures of the brain and mental retardation in children with Down syndrome (r – Spearman rank correlation coefficient)

Structure	*r*	*t*-value	*p*-value
Right amygdala	–0.030	–0.138	0.892
Right hippocampus	–0.441	–2.252	0.035
Left amygdala	–0.132	–0.611	0.548
Left hippocampus	–0.216	–1.012	0.323
Total brain volume	–0.058	–0.268	0.791
Right temporal lobe	0.050	0.228	0.821
Left temporal lobe	0.177	0.824	0.419
Right frontal lobe	–0.360	–1.768	0.092
Left frontal lobe	–0.316	–1.528	0.141

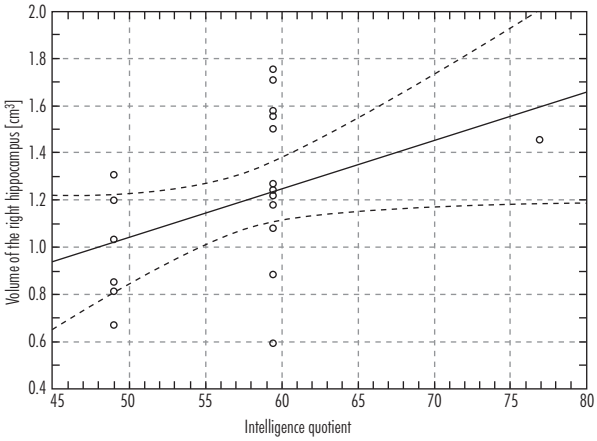

Fig. 3. Correlation between volume of the right hippocampus and mental development of children with Down syndrome ($r = –0.441$, $p = 0.035$)

those of the matched comparison subjects. Amygdala volumes of the non-demented DS subjects did not differ from those of the comparison subjects. As with the hippocampus, amygdala volumes did not decrease with age among the non-demented DS subjects. These findings suggest that the amygdala is proportionate to total brain volume during development, but that specific atrophy of the amygdala, like that of the hippocampus, is involved in the dementia experienced by elderly persons with DS. Subjects with DS who were diagnosed as demented had significantly smaller volumes of the hippocampus and amygdala than those who were not demented.

Pinter *et al.* [3] indicated that hippocampal volumes were decreased out of proportion to overall brain volumes in children with DS, whereas adjusted amygdala volumes did not differ significantly from controls. These results are consistent with a recent study that reported similar hippocampal volume decreases and no significant differences in amygdala volumes, among non-demented adults with DS [26].

Frontal lobe volumes also were significantly smaller in the subjects with DS [3]. These findings are in agreement with our report. The frontal lobes have been frequently implicated in the cognitive deficits of DS, including executive dysfunction, inattention, and a tendency toward perseveration.

Haier *et al.* [19] in patients with DS found less grey matter in several areas throughout the brain, including the cerebellum, anterior cingulate, frontal lobe and temporal lobe, including part of the hippocampus. In the present study, we did not assess the grey matter in the tested brain areas.

In regard to our study of structures involved in the language deficits of DS, we found neuroimaging evidence for our hypothesis of smaller overall temporal lobe volumes. The possibility of an association between smaller regional volumes and cognitive dysfunction is supported by previous studies [3,21]. Selective smaller hippocampal volumes shown in MRI studies of adults with DS [27] and in our report have highlighted the possibility that important temporal lobe subregional volume abnormalities in either direction may be present throughout development and may contribute to language and memory deficits.

In another study among patients with DS [26], smaller volumes of the right and left amygdala, hippocampus, and posterior parahippocampal gyrus were significantly associated with older patients. Teipel *et al.* [28] reported that DS subjects showed a significant correlation between hippocampus volume and age. They reported correlations between age and corpus callosum areas, most prominent in posterior sub-regions, in the DS subjects. The age-related decrease of corpus callosum area was comparable to the decrease of hippocampal volume.

MRI volumetric studies of both subjects with AD [4,29] and DS with dementia [26] have revealed dramatic volume decreases in the amygdala and hippocampus. These results raised the possibility that the hippocampal volume decreases seen in studies of non-demented adults with DS might represent a presymp-

tomatic stage of volume loss associated with early AD pathology.

Contrary to the decreased hippocampal volumes apparently present from early childhood, after adjustment for total brain volume, amygdala volumes in subjects with DS in our study did not differ significantly from those of controls [3,28].

The strengths of our study include our relatively large group size and its wide age range, which also included children under the age of five. We did not test the cerebellum, parietal and occipital lobes, and sub-cortical structures in children with DS, and this may be considered a limitation of our study.

Our results confirm the results of previous studies with respect to overall patterns of brain volumes in children with DS. Further studies are needed to investigate the volumes of the cerebellum, the parietal and occipital lobes, and sub-cortical structures.

Conclusions

1. Total brain volume in children with DS was significantly lower compared with controls. It was associated with significantly lower volume of the frontal and temporal lobes, including the right and left hippocampus and amygdala.
2. We also found a negative correlation between mental retardation and volume of the right hippocampus.
3. The presence of these abnormalities from an early age contributes to the specific cognitive and developmental deficits seen in children with DS.

Disclosure

The authors report no conflict of interest.

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