Katarzyna ANNA DYLĄG[1,2]
Aleksanda SIKORA-SPOREK[2]
Bożena BAŃDO[2]
Joanna BOROŃ-ZYSS[2]
Dorota DROŻDŻ[1]
Paulina DUMNICKA[3]
Katarzyna PRZYBYSZEWSKA[2]
Mateusz SPOREK[4]
Jerzy W. WALOCHA[4]
Wadim WOJCIECHOWSKI[5]
Andrzej URBANIK[5]

Magnetic resonance imaging (MRI) findings among children with fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS) and alcohol related neurodevelopmental disorders (ARND)

[1]Department of Pediatric Nephrology, Jagiellonian University Medical College, Krakow, Poland
Head:
Prof. dr hab. med. *Jacek A. Pietrzyk*

[2]St.Louis Children Hospital

[3]Department of Medical Diagnostics, Jagiellonian University Medical College, Krakow, Poland
Head:
Dr hab. n. med. *Ryszard Drożdż*

[4]Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland
Head:
Prof. dr hab. med. *Jerzy A. Walocha*

[5]Department of Radiology, Jagiellonian University Medical College, Krakow, Poland
Head:
Prof. dr hab. med. *Andrzej Urbanik*

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Adres do korespondencji:
lek. Katarzyna Dyląg
Wojewódzki Specjalistyczny Szpital Dziecięcy im. Św Ludwika
ul. Strzelecka 2, 31-503 Kraków
Ph.no.+48505326854
e-mail: katarzyna.anna.dylag@doctoral.uj.edu.pl

Background: The aim of the study was to analyze the findings in MRI (magnetic resonance imaging) of the brain amongst children diagnosed with fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS) or alcohol related neurodevelopmental disorders (ARND). The issue has been studied in several researches previously but the experts agree that there is still few data on the MRI results in the group of younger children.

Material and Methods: MRI results of 121 patients with either FAS or pFAS or ARND diagnosed with Canadian criteria were analyzed regarding the presence of abnormalities. The group consisted of 71 patients diagnosed with FAS, 33 diagnosed with pFAS and 17 diagnosed with ARND. The mean age of the patients was 8.03 years (standard deviation 4.07).

Results: In the total group of FASD patients 61.98% of the patients' MRI results were abnormal. The most common abnormality in MRI of the patients were demyelination plaques (incidence 23.1%) and corpus callosum narrowing (20.7%) as well as ventricular asymmetry (18.8%).The demyelination plaques and corpus callosum narrowing were more frequent among children ≤4 years old (41.7% vs 18.6%; p=0.016 and 50.0% vs.13.4%; p<0.001, respectively). Age ≤4 years predicted the presence of demyelination plaques and corpus callosum narrowing independently of FAS diagnosis. Among younger children, multiple central nervous system abnormalities were observed more often than in the older age group (54.2% vs. 14.4%; p<0.001). Odds ratio for multiple changes was 0.84 per one-year increase in age (95% CI 0.73-0.97), p=0.016. Furthermore, in the analysis according to the specific diagnosis,

Wstęp: Celem badania była ocena nieprawidłowości znalezionych w badaniu rezonansu magnetycznego mózgowia u dzieci z płodowym zespołem alkoholowym (fetal alcohol syndrome - FAS), częściowym płodowym zespołem alkoholowym (partial fetal alcohol syndrome - pFAS) i neurorozwojowymi uszkodzeniami związanymi z narażeniem na alkohol (alcohol related neurodevelopmental disorder - ARND). Problem ten poruszano w wielu badaniach, ale według ekspertów wciąż brakuje doniesień obejmujących grupę młodszych dzieci.

Materiały i metody: Analizie poddano wyniki badania rezonansu magnetycznego u 121 pacjentów, którym postawiono rozpoznanie FAS, pFAS lub ARND według kryteriów kanadyjskich. Grupa obejmowała 71 pacjentów z FAS, 33 z pFAS, 17 z ARND. Średnia wieku wynosiła 8,03 roku (odchylenie standardowe 4,07).

Wyniki: Nieprawidłowości w badaniu stwierdzono u 61,98% pacjentów. Zmiany demielinizacyjne (częstość 23,15) oraz zwężenie ciała modzelowatego (20,7%) i asymetria komór (18,8%) charakteryzowały się największą częstością występowania. Zmiany o typie demielinizacji oraz zwężenie ciała modzelowatego występowały istotnie częściej w grupie dzieci ≤ 4 roku życia (odpowiednio: 41,7% vs.18,6% p=0,016 oraz 50,0% vs.13,4%; p<0,001). Wiek ≤ 4 roku życia był czynnikiem prognostycznym dla występowania zmian demielinizacyjnych oraz zwężenia ciała modzelowatego niezależnie od rozpoznania FAS. W grupie młodszych dzieci częściej niż u starszych dzieci obserwowano mnogie nieprawidłowości ośrodkowego układu nerwowego w badaniu rezonansu magnetycznego (54,2% vs. 14,4%; p<0,001). Iloraz

among the patients diagnosed with FAS, multiple anomalies were more common than in pFAS and ARND. Both age ≤4 years and FAS diagnosis were independent predictors for multiple anomalies in multiple logistic regression.

Conclusion: In structural brain MRI of younger children, multiple anomalies were found more frequently than among older children. Demyelination plaques and corpus callosum narrowing were more common in younger FASD patients than in older ones.

szans dla mnogich nieprawidłowości ośrodkowego układu nerwowego wynosił 0,84 wraz z wzrostem wieku o rok (95% CI 0,73-0,97), p=0,016. W analizie w zależności od rozpoznania klinicznego, mnogie zmiany w ośrodkowym układzie nerwowym obserwowano częściej u pacjentów z FAS niż z pFAS i ARND. Zarówno wiek ≤ 4 roku życia, jak i rozpoznanie FAS stanowiły niezależny czynnik prognostyczny mnogich zmian ośrodkowgo układu nerwowego w wielorakiej regresji logistycznej.

Wnioski: W rezonansie magnetycznym mnogie nieprawidłowości w ośrodkowym układzie nerwowym obserwowano częściej u młodszych dzieci w porównaniu ze starszymi. Zmiany demielinizacyjne i zwężenie ciała modzelowatego charakteryzowały się większą częstością w grupie młodszych pacjentów z FASD.

Introduction:

The negative effect on the fetus of alcohol consumed by the mother was first mentioned in the Bible [1]. The attention of medical professionals was dragged to this topic at the beginning of 18th century in Great Britain, in the time of "gin epidemic", when The Royal College of Physicians warned the Parliament that gin was "*too often the cause of weak, feeble, and distempered children, who must be, instead of an advantage and strength, a charge to their country*" [2]. Although the first symptoms of Fetal Alcohol Syndrome (FAS) were described in the medical literature in the nineteenth century in France [3], the syndrome itself was defined in seventh decade of 20th century [4]. Moreover, term fetal alcohol spectrum disorders (FASD) proposed by A. Streissgut et al. covers three terms: FAS (Fetal Alcohol Syndrome), pFAS (partial Fetal Alcohol Syndrome) and ARND (Alcohol Related Neurodevelopmental Disorders) [5]. FASD is currently thought to be the leading cause of intellectual disability in the developed countries [6]. The prevalence of FASD in the United States of America is estimated on 1-3 per 1000 live births [7] but in high-risk communities it can be as high as 10-15 per 1000 live births [8]. According to the recently published study, the prevalence of FASD in Poland is considered to be greater than 2% [9].

The toxic effect of the alcohol consumed by a pregnant woman on the fetal cells is the only cause of FASD. The main results of this process are: central nervous system damage, small gestational age or/and failure to thrive or characteristic facial dysmorphy. The underlying processes causing neurodevelopmental disability among persons with FASD are caused by extensive fetal cells apoptosis mainly throughout free radicals' activation [10]. Another mechanism in which alcohol affects the developing brain is the growth factor production disruption what results in inhibition of cell proliferation. Moreover, both in vitro and in vivo studies have shown that astrocyte formation and proliferation is also impaired due to the alcohol exposure [10]. Not only the number of the cells in the central nervous system can be affected by alcohol, though. It has been proven that the neurotransmitters such as serotonin and glutamate synthesis and their receptors development impairment occur as the result of alcohol exposure [10]. Finally, alcohol influences negatively genes expression and adhesive molecules synthesis [10]. All of the mechanisms mentioned can result in both structural and functional damage of central nervous system of children with FASD.

The studies on animal models [11] has shown that holoprosencephaly [12], decrease of cerebral volume and increase in septal volume [13] as well as ventricular dilatation [14] can occur among individuals exposed to alcohol prenatally more commonly than in the healthy population.

The development of imaging techniques has drawn the attention of the scientists to the central nervous system abnormalities among persons with FASD. The research on the fetal brain prenatal ultrasound imaging has shown that in children exposed on the alcohol presented shorter frontothalamic distance in the second and third semester compared to the control group [15]. Bookstein et al. made an attempt to detect characteristic features of FASD in neonatal transfontanelle brain ultrasound finding that some of the measurements of corpus callosum are abnormal in these patients [16].

In the studies using the MRI technique to imagine the brain- the microcephaly reflecting smaller total brain volume was described as the common characteristic of FASD patients not only in the clinical examination but also in the MRI [17]. Decrease in gray matter was also observed [18]. Focally, smaller volume of the basal ganglia especially caudate, hippocampus and frontal cortex were also noticed in many studies [19]. The midline brain anomalies [20,21] especially the narrowing of corpus callosum were proven to be associated with prenatal alcohol exposure in many researches and were considered as a potential marker sign of FAS [22]. Although the structural abnormalities of the brain of children with FASD were studied many times, the researchers emphasize that the data in the group of young children is still scarce [18].

The purpose of our study was to analyze the brain structure in MRI in the patients of our center.

Material and Methods

Subjects

The study was performed as a retrospective study. Patients of Multidisciplinary FASD Diagnostic Center, who had the central nervous system MRI done in the process of diagnosis, were included in the study. MRI results of 121 children (48 girls, 73 boys), 71 diagnosed with FAS, 33 diagnosed with pFAS and 17 diagnosed with ARND were analyzed. The mean age of the patients was 8.03 years (standard deviation 4.01).

Methods

In the process of diagnosis patients were examined by pediatrician, children psychiatrist, pediatric neurologist and psychologist. The diagnosis was established by the diagnostic team on the basis of Canadian criteria [23]. According to these criteria, FAS can be diagnosed if the child presents with: failure to thrive/small birth weight, presence of three main facial dysmorphies and the evidence of damage in central nervous system noticeable either in neurological examination or/and psychological tests. The characteristics crucial to diagnose pFAS are: two of three main facial dysmorphies, and the evidence of damage in central nervous system noticeable either in neurological examination or/and psychological tests. To be diagnosed with ARND the patient has to present with neurodevelopmental disorders in psychological examination. For the diagnosis of pFAS and ARND the prenatal alcohol exposure has to be confirmed.

MR examinations were performed with a 3.0-T scanner (Philips Achieva 3.0T TX, Philips). The protocol consisted of sequences: Dual (PD+T2W), TSE T1W, 3D TFE T1W, FLAIR, DWI (with ADC maps) and 3D TFE T1 and TSE T1W after intravenous administration of contrast agent with Magnevist (Bayer Schering Pharma, Berlin, Germany) 0.1 mmol/kg injection. The MRI's were interpreted by trained and experienced radiologist.

Ethics

The study protocol was approved by the local ethical committee. The study complies with Declaration of Helsinki.

Statistical analysis

Means and standard deviations were reported for continuous variables. Categorical variables were described as counts and percentages. Contingency tables were analyzed using chi-squared test. Simple and multiple logistic regression was used in order to determine odds ratios (OR) for abnormalities of central nervous system; the OR were reported with 95% confidence intervals (95% CI). All the tests were two-tailed and the results were considered significant at $p<0.05$. The data were processed using STATISTICA software (StatSoft, Inc., Tulsa, USA), version 12.

Table I
Group characteristics.
Charakterystyka badanej grupy.

	age <4	Age >4
Females	52%	37%
Males	47%	62%
FAS	84%	54%
pFAS	10%	30%
ANRD	6%	16%

Table II
Incidence of MRI abnormalities in all the patients.
Częstość występowania poszczególnych zmian w obrazie MRI mózgowia badanych pacjentów.

Abnormality	total
Demyelination plaques	23.14%
Corpus callosum narrowing	20.66%
Cerebral ventricles asymmetry	18.18%
Vascular malformations	6.61%
Pineal gland cyst	5.79%
Adenoid overgrowth	2.47%
Arachnoid cyst	2.47%
Gray matter heterotopia	2.47%
Porencephaly	1.65%
Cyst of the septum pellucidum cave	1.65%

Table III
Incidence of MRI abnormalities in the age subgroups p-reflects the comparison of the two age subgroup.
Częstość poszczególnych zmian w obrazie MRI mózgowia w podgrupach wiekowych p- odzwierciedla różnice w dwóch podgrupach wiekowych.

Abnormality	≤ 4 years old (N=24)	> 4 years old (N=97)	p
Demyelination plaques	41.67%	18.56%	0.016
Corpus callosum narrowing	50.00%	13.40%	<0.001
Cerebral ventricles asymmetry	12.50%	19.59%	0.42
Vascular malformations	0.00%	8.25%	0.14
Pineal gland cyst	4.35% 4.17%	6.12% 6.19%	0.70
Adenoid overgrowth	4.17%	2.06%	0.55
Arachnoid cyst	4.17%	2.06%	0.55
Gray matter heterotopia	4.17%	2.06%	0.55
Porencephaly	4.17%	1.03%	0.28
Cyst of the septum pellucidum cave	4.17%	1.03%	0.28

Table IV
Localisation of demyelination plaques.
Lokalizacja zmian demielinizacyjnych.

Localisation of demyelination plaques	Frequency
Frontal lobes	54%
Parietal lobes	36%
Ooccipital lobes	21%
Corpus callosum	4%
Semioval center	7%
Brainstem	4%
Diffuse	25%

Results

In the total group of FASD patients 61.98% of the patients' MRI results were abnormal. The most common abnormality found in the MRI were demyelination plaques with the incidence 23.1%, followed by corpus callosum narrowing (incidence 20.7%) and cerebral ventricles asymmetry (incidence 18.8%). The anomalies seen less frequently were: vascular malformations, pineal gland cyst, arachnoid cyst, gray matter heterotopia, porencephaly, cyst of the septum pellucidum cave (Tab. II). There were single cases of pituitary adenoma, Dandy-Walker syndrome, Sylvian fissure asymmetry.

The MRI abnormalities were analyzed in the age sub-groups.The demyelination plaques turned out to be more frequent among children less than and equal to the age of 4 years (41.7% vs 18.6%; p=0.016). The corpus callosum narrowing was also more common in the group of younger children (50.0% vs. 13.0% p<0.001). Age ≤4 years predicted the presence of demyelination plaques (OR 2.94; 95% CI 1.10-7.83; p=0.030) and corpus callosum narrowing (OR 5.97; 95% CI 2.17-16.44; p<0.001) independently of the diagnosis of FAS. The other abnormalities were equally frequent in both age groups (Tab. III). Moreover, the two main abnormalities were not equally prevalent in both age groups- demyelination plaques were more frequent in older children than corpus callosum narrowing (Tab. III). The demyelination plaques were mainly located in frontal (54%), parietal (36%) and occipital (21%) lobes of the brain. 4% of them were located in corpus callosum, 7% in semioval center. In 25% of MRI they were additionally described as diffuse (Tab. IV).

Among younger children (i.e. ≤4 years of age), co-occurring multiple central nervous system abnormalities were observed more often than in the older age group (54.2% vs. 14.4%; p<0.001) (Fig. 1). Odds ratio for multiple changes was 0.84 per one-year increase in age (95% CI 0.73-0.97; p=0.016). Furthermore, in the analysis according to the specific diagnosis, among the patients diagnosed with FAS, multiple anomalies were more common than in the pFAS and ARND patients (31% vs. 9 % vs. 11.8% respectively). Both age ≤4 years (OR 6.19; 95% CI 2.23-17.21; p<0.001) and FAS diagnosis (OR 3.43; 95% CI 1.13-10.47; p=0.028) were independent predictors for multiple anomalies.

Diccussion

Our study results confirm that corpus callosum abnormalities are among those mainly observed in the group of patients prenatally exposed to alcohol. However, Johnson et al. [24], Mattson et al. [25], Riley et al. [20], and Swayze et al. [23] have described total agenesis of corpus callosum in their work. In our study we have only observed corpus callosum narrowing. Regarding the prevalence- Astley et al. [26] reported abnormal corpus callosum size in 9-15% of patients (depending on the subregion), in the Swedish study 2 of 17 children (11.7%) had the corpus callosum hypoplasia [27]. We report significantly higher prevalence of corpus callosum narrowing/hypoplasia.

Interestingly, the abnormality with the higher incidence were the demyelination plaques. In the previous studies on the population of the children prenatally exposed to alcohol disruptions of the myelination process or demyelination were only mentioned by two researchers. Riikonen et al. has reported delayed myelination in 2 children in the study on 11 subjects [28]. Sowell at.al. interpreted the increased cortical thickness, they have found in the group of children with heavy prenatal alcohol exposure, as decreased myelination [29]. The possible explanation of the finding can lie in the mechanism of the damage done by the alcohol to the brain cells. It has been well established that alcohol consumption can lead to demyelination in adults [30,31]. Fetal brain can be much more susceptible to the alcohol exposure. Moreover, the studies proved that malnourishment of the mother can affects the fetal brain resulting in demyelination or delayed myelination [32]. As people addicted to the alcohol are often malnourished we hypothesize that several factors might have influenced the brain of the children among whom demyelination has been observed. The matter requires further research. In the other possible interpretation of our results, demyelination plaques could be a characteristic feature confirming one the FASD diagnosis in young children. To determine whether the plaques are caused by demyelination or decreased myelination the MRI should be repeated in few years. A prospective study on this group of patients would give an answer to this question. The research should be also continued to correlate neurobehavioral tests results with the localization of the demyelination

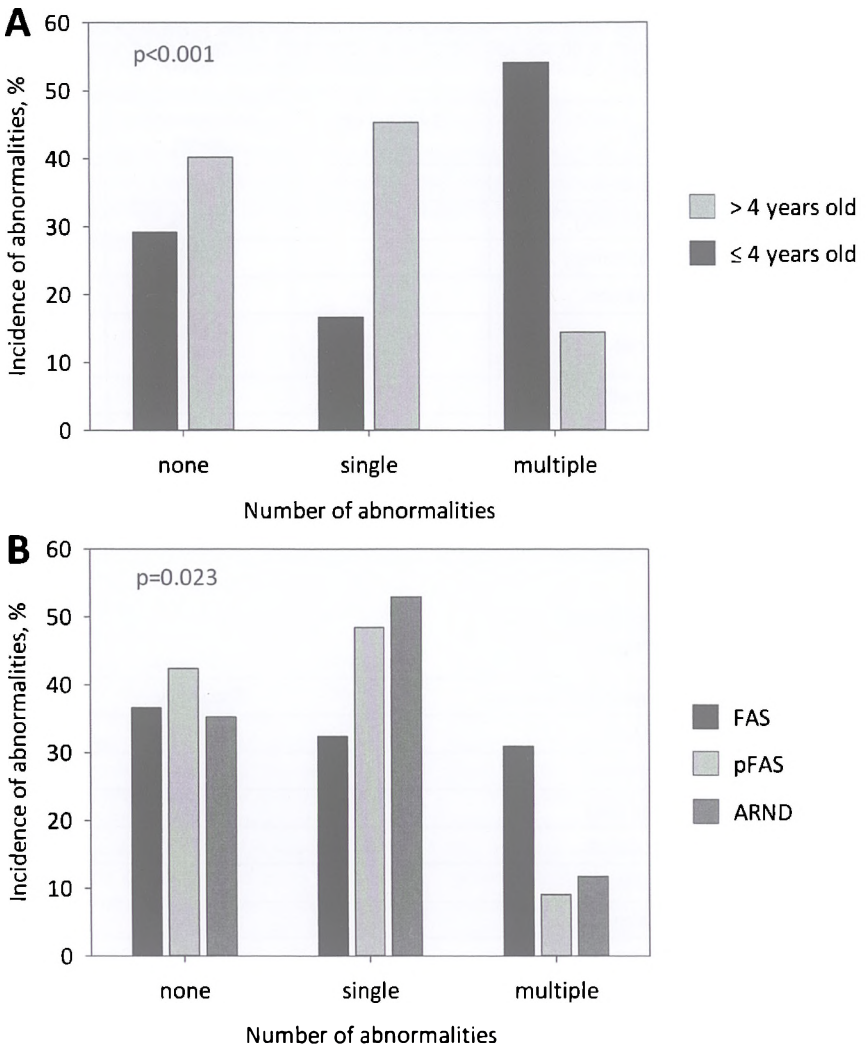

Figure 1

Incidence of abnormalities in structural MRI according to A - age, B - diagnosis.

Częstość zmian w obrazie MRI w zależności od A - wieku, B - rozpoznania.

plaques in MRI.

The other abnormalities observed in our group of patients were mentioned in the researchers before. Riikonen et al. reported ventricular asymmetry [28], Sowell et al. reported abnormalities of gray matter structure [33], Jégou et al. reported brain vasculature malformations [34], Peiffer et al. reported porencephaly [35] . The pineal gland cyst and adenoid overgrowth are the conditions with relatively high prevalence among otherwise healthy children [36,37] so they could be interpreted as accidental findings.

Archibald et al. [38], Mattson et al. [25], Nardelli et al. [39], Riikonen et al. [28], Roussotte et al. [40] have described reduction in size of basal ganglia, while in the studies performed by: Astley et al. [28], Archibald et al. [38], Joseph et al. [41], Nardelli et al. [39], Riikonen et al. [28] there were evidence on hippocampus damage. What is interesting, in none of our patients' MRI's, similar abnormalities could have been observed.

The fact that in the group of the children younger than 4 years old multiple abnormalities were much more common than in the older ones is an important finding of our study. On one hand it can be affected by the fact that the disabilities may remain undercover to the school age, so infants and toddlers referred to the hospital may have suffered from more severe, symptomatic brain damage. On the other hand some of the abnormalities may resolve spontaneously [42-44] so further research should be continued to verify whether among FASD patients the process can occur.

Conclusion

Demyelinating plaques, corpus callosum narrowing and ventricular asymmetry were characterized by the highest incidence in structural brain MRI of FASD patients. In the group of younger children multiple anomalies were found more frequently than among older children. Demyelination plaques and corpus callosum narrowing, were more common in younger FASD patients than in the older ones.

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