Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"

Journal Homepage: http://cjns.gums.ac.ir

Research Paper

The Impact of Delivery Mode on the Development of Behavioral Disorders in Children

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Citation Sedighinejad A, Zavarmousavi SM, Soltanipour S, Naderi Nabi B, Safari Moghadam F, Shahrokhi Rad R, Biazar G. The Impact of Delivery Mode on the Development of Behavioral Disorders in Children. Caspian J Neurol Sci. 2024; 10(4):341-346. https://doi.org/10.32598/CJNS.10.39.513.1

Running Title Mode of Delivery and Behavioral Disorders

https://doi.org/10.32598/CJNS.10.39.513.1

Article info:
Received: 24 Jul 2024
First Revision: 02 Aug 2024
Accepted: 28 Sep 2024
Published: 01 Oct 2024

ABSTRACT

Background: Existing evidence on the relationship between mode of delivery and offspring's emotional and behavioral problems is limited and inconsistent.

Objectives: This study investigated the relationship between anesthesia during childbirth and behavioral disorders in children.

Materials & Methods: This research was conducted at psychiatric clinics affiliated with Guilan University of Medical Sciences (GUMS), Rasht City, Iran. The studied population consisted of children who were diagnosed with autism spectrum disorder, attention-deficit/hyperactivity disorder, and oppositional defiant disorder based on diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) criteria. For each case, a healthy sibling was considered as a control group. We completed a checklist containing the type of delivery, including normal vaginal delivery (NVD), cesarean section (CS) under general anesthesia (GA) or spinal anesthesia (SA), and painless labor, as well as neonate birth status (term/preterm).

Results: In this study, 720 children aged 4-18 were enrolled. No significant difference was observed in terms of birth status (term or preterm) (P=0.482), age (P=0.464), and mode of delivery (P=0.236), while the difference was significant regarding gender (P=0.001) and type of anesthesia (P=0.0001). So, delivery under GA was significantly associated with behavioral disorders compared to NVD or CS under SA (P=0.0001). The logistic regression test demonstrated that CS under GA increases 2.74 times the likelihood of later development of behavioral disorders.

Conclusion: Children born by elective CS under GA may face childhood behavioral problems. Further investigation is needed to support these findings in other populations and explore the potential biological mechanisms.

Keywords: Child, Behavioral problems, Obstetric

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Highlights

• This study aimed to assess the relationship between behavioral disorders and fetal exposure to anesthetic agents according to the mode of delivery.

• Despite the alarms about the issue of general anesthesia (GA)-related neurotoxicity in developing brains and universal interest, the subject has not been sufficiently investigated in Iran.

• A positive relationship was found between behavioral disorders and male gender and delivery under GA.

Introduction

Families of children with behavioral disorders face many out of ordinary challenges that may result from the child's conditions or adverse reactions and stigma from society. Social arrangements often do not consider their needs and interests [1]. Studies have shown that the treatment of behavioral disorders in children is challenging and not consistently successful [2]. Decades of research have demonstrated multiple risk factors for behavioral disorders beyond genetics [3]. Nagata et al. showed a strong association between social media, screen time and new-onset behavior disorders [4]. Another study emphasizes the critical importance of the time of exposure and the vulnerability of the developing brain to anesthetics [5]. Lähdepuro et al. demonstrated that behavioral disorders in children were related to adverse maternal mental health during pregnancy [6]. Madigan et al. [7] Robinson et al. [8] and Van den Bergh et al. [9] reported similar results. This evidence suggests that exposure of the developing brain to environmental factors may program the brain differently and increase the risk of behavioral disorders [9-11].

Recently, the association between early general anesthesia (GA) exposure and behavioral disorders has been widely discussed. Studies demonstrate that children who were born by cesarian section (CS) under GA are at higher risk of autism spectrum disorder (ASD), emphasizing GA-related neurotoxicity [12, 13]. Experimental studies have also supported this hypothesis [14, 15]. Furthermore, studies have demonstrated other problems besides behavioral disorders, including maternal postpartum mood disorders [16], infants' skin and gastrointestinal issues [17], and neurocognitive development in children [18]. Despite the alarms about the issue of GA-related neurotoxicity in developing brains and FDA recommendation [19], the subject has not been thoroughly investigated in Iran [20].

Considering the problems that the family and child with behavioral disorder are dealing with, as well as the financial burden of these children on society and given the contradictory results of the related studies [21], this research was designed. Behavioral disorders are multifactorial, and some predisposing factors are preventable, while others, such as season of birth, gender and genetics, are not. The mode of delivery and the type of anesthesia are among the factors that can be selected to some extent [22, 23]. In this study, we investigated the issue of behavioral disorders from the aspect of fetal exposure to anesthetic agents according to the mode of delivery.

Materials and Methods

This study was performed in academic psychiatric clinics, Shafa and Besat, Rasht City, Iran, affiliated with Guilan University of Medical Sciences (GUMS) from February 2022 to May 2024. The study was approved by the University Research Ethics Committee. First, the medical student of the research project screened the medical files of children to identify and sort out those with ASD, attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder diagnoses.

Through telephone interviews, the purpose of the study was explained to the parents, and if they agreed to participate, they were included in this research. Due to the genetic background of these diseases, a healthy sibling was also included in the study as a control group for each case. Afterward, a checklist containing questions about the type of delivery, including normal vaginal delivery (NVD), CS under GA or spinal anesthesia (SA), painless labor, and neonate birth status (term/preterm), was completed by the responsible medical student.

The inclusion criteria comprised children aged 5-18 diagnosed with ASD, ADHD, or oppositional defiant disorder based on the diagnosis of a pediatric psychiatry specialist. The diagnosis was performed according to diagnostic and statistical manual of mental disorders, ^{5}th edition (DSM-5) criteria.

Table 1. Children's characteristics of two groups of case and control (n=360)

Variables	Status	No. (%)/Mean±SD		P
		Case Group	Control Group	
Gender	Male	180(44.6)	224(55.4)	<0.001
	Female	180(57)	136(43)	
Age (y)	5-9	82(48.5)	87(51.5)	0.564
	9-13	147(52.5)	133(47.5)	
	13-18	131(48.3)	140(51.7)	
Age (y)	Min-max	3.03±12.2	3.36±12. 3	0.464
Birth status	Term	322(50.5)	316(49.5)	0.482
	Preterm	38(46.3)	44(53.7)	
CS		258(48.7)	272(51.3)	0.236
NVD		102(53.7)	88(46.3)	

CS: Cesarean section; NVD: Normal vaginal delivery.

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The exclusion criteria comprised the unwillingness of parents to participate in the research or lacking healthy siblings in the family.

Statistical analysis

The data were entered into SPSS software, version 21. Mean±SD were used to describe the data. If the data were normally distributed, the independent t-test. The equivalent non-parametric test was used in non-normal distribution. The chi-square test or Fisher exact was used for frequency comparisons between the case and control groups. Finally, logistic regression analysis was used. Statistical significance was determined as P<0.05.

Results

Finally, the data from 720 children (360 cases and 360 controls) with a mean age of 12.21±3.20 years were analyzed. Comparing the two groups, no significant difference was observed in terms of birth status (term or preterm) (P=0.482), age (P=0.464), and mode of delivery (P=0.236). However, a significant difference was detected regarding gender (P=0.001) and type of anesthesia (P=0.0001). Thus, delivery under GA was positively associated with behavioral disorders compared to other modes of delivery, including NVD or CS under SA (Tables 1 and 2). To control the confounding variables and obtain the odds ratio of each investigated factor, the 4-mode of delivery variables was converted into two modes, including two groups of receiving anesthesia or not, and then entered into the model along

Table 2. Birth via different modes of delivery in two groups of case and control (n=360)

Status	No. (%)		P
	Control Group	Case Group	
SA	106(65)	57(35)	<0.001
GA	154(41.4)	218(58.6)	
Painless labor	10(62.5)	6(37.5)	
NVD	90(53.3)	79(46.7)	

SA: Spinal anesthesia; NVD: Normal vaginal delivery; GA: General anesthesia.

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Table 3. Odds ratio and CI of predictors for behavioral disorders

Step 1[a]	B (SE)	OR	95% CI[b] for Exp[b]		P
			Lower	Upper	
Constant	-1.226(0.501)	0.294	-	-	0.014
Gender (Male)	0.499(0.155)	1.647	1.215	2.234	0.001
Born status (Term)	0.317(0.253)	1.373	0.837	2.254	0.209
Type of delivery (CS[c])	0.580(0.233)	1.786	1.132	2.821	0.013
Type of anesthesia (General)	1.010(0.199)	2.746	1.858	4.060	0.000

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[a]Variables entered on step 1: Gender, birth status, delivery, anesthesia, [b]Logistic regression test (Backward LR), [c]Cesarean section.

with other variables. The logistic regression model revealed that male gender, exposure to GA and CS were significantly associated with the development of behavioral disorders with odds ratios of 1.64, 1.78, and 2.74, respectively (Table 3).

Discussion

We found that more behavioral disorders were reported when GA was chosen for CS and boys also showed more vulnerability. Previously, we conducted a study to investigate the relationship between ADHD and early exposure of the developing brain to anesthetics. Similarly, boys were significantly more affected than girls [24]. A recent meta-analysis reported that compared to children born via NVD, children born by CS showed an increased risk of ASD and ADHD [25]. Chien L-N et al. compared the effect of CS under GA and regional anesthesia (RA) and NVD in developing ASD. They showed that ASD was significantly more common among children who underwent CS under GA than RA. However, there was no difference between CS by RA and NVD. This finding is a self-confirmation of the harmfulness of anesthetic drugs in the early stages of life [13]. This study also supported the study conducted by Samuel, who found that birth via CS under GA was associated with the development of ASD. Emphasizing the hypothesis that early brain exposure to anesthetic agents could be harmful [26]. In a contrasting study, Maher et al. examined the association between mode of delivery and behavioral disorders in children aged between 3 and 17 years at six time points. They reported that the delivery mode did not significantly impact behavioral problems [23]. Grisbrook et al. and Künzel found no associations between delivery mode and behavioral disorders [16, 27]. As mentioned, there is a discrepancy among human studies. Conducting human studies creates some challenges. It is difficult to match the studied groups in terms of genetics, socioeconomic status and the type and dose of anesthetics, all of which are among the influential factors. Also, differences in the methodology and design of the studies should be considered. As in the Wen-Ru-Ko study, only children referred to health assessment centers were investigated [28]. In Sprung's study, the information was based on samples collected from all over the country [29]. Furthermore, how the behavioral disorders diagnosed is also important, which could be done by neurologists, psychiatrics, or pediatricians. Therefore, there is a possibility that all diagnostic criteria were not strictly followed. In the current study, the diagnosis was made by an expert pediatric psychiatrist. Another issue that arises is to what extent behavioral disorders can be attributed to anesthetic drugs. So that, a child who needs surgery and GA at a young age may suffer from co-morbidities and gets sick in general. Studies have shown that any systemic inflammation can affect the developing brain. Therefore, surgery itself can also cause systemic inflammatory and stress responses. In general, it is believed that behavioral disorders cannot be attributed only to neurotoxicity caused by anesthetic drugs [30, 31].

Conclusion

The study found a significant association between anesthesia exposure during delivery and later behavioral disorders. The male gender seemed to be more vulnerable to this process. This research confirmed the studies that emphasized the possibility of neurotoxicity of anesthetic drugs in the developing brain. Considering the limited number of research studies and many confounding factors in forming behavioral disorders, conducting well-planned prospective cohort studies is recommended.

Study limitations

Due to the nature of a retrospective study, we acknowledge some limitations. Valid information about influential factors such as birth hypoxia, Apgar score, jaundice, and birth weight was not provided. Furthermore, parental forgetfulness should be considered.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1400.533).

Funding

The paper was extracted from the PhD dissertation of Fatemeh Safari Moghadam, approved by Research Council of Gilan University of Medical Sciences (Grand No.: 1400092211).

Authors contributions

Conceptualization and study design: Abbas Sedighinejad and Reyhaneh Shahrokhi Rad; Data Analysis and interpretation: Soheil Soltanipour and Bahram Naderi Nabi; Data collection: Fatemeh Safari Moghadam and Seyedeh Maryam Zavarmousavi; Statistical analysis: Soheil Soltanipour; Critical revision: Gelareh Biazar; Final approval: Abbas Sedighinejad and Reyhaneh Shahrokhi Rad.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors sincerely express their gratitude for the valuable support of the esteemed Vice President of Research and Technology at Guilan University of Medical Sciences, Mahin Tayefeh Ashrafieh, and Zahra Khosnoudi, experts at the Anesthesia Research Center. The authors also want to thank all the parents who participated in this study.

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