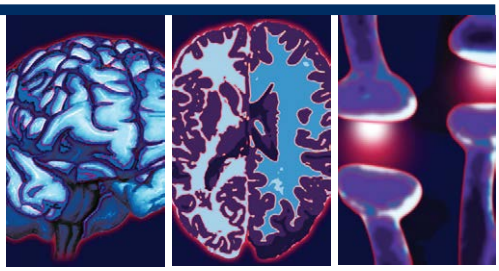
Case Report



Circulating FABP4 May Predict Pre-Malformation Fetus in Pregnant Patient with Epilepsy

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Abstract

This report aimed to assess the potential association between blood fatty acid binding protein 4 (FABP4) and epileptic pregnant woman. Plasma FABP4 content was determined in pregnant women with and without epilepsy during second-trimester embryo (around 4-month fetus). In addition to other comparable clinical parameters, plasma FABP4 was reduced in pregnant woman with epilepsy when referenced to that in epilepsy-free control. It was characterized with imageologically detectable pre-abnormality of fetus, but other clinically diagnosed parameters were inconspicuous. Therefore, blood FABP4 reduction independently predicted fetal pre-abnormality in epileptic pregnant woman. Potentially, circulating FABP4 may function as a promising biomarker for pre-malformation fetus in epileptic pregnant woman.

Keywords

Fatty acid binding protein 4, Epilepsy, Fetus

Introduction

Epilepsy is one of the most common neurologic disorder, and the majority of affected people are expected to participate fully in life experiences, including childbearing [1]. Increasing evidences indicate that anticonvulsant drug exposed to pregnant women results in unwanted damage to the fetus [2]. However, limited methods are used to screen these malformations induced by epilepsy-controlled medications, especially for pregnant patients. Fatty acid binding protein 4 (FABP4) refers to a cellular lipid chaperone involved in coordination of lipid transportation [3]. And FABP4 is primarily expressed in adipocytes and can be released into the circulation [4]. In the nonpregnant state, FABP4 is associated with the following potential risk factors: obesity, hypertension, and diabetes [5,6]. Our previous study highlights that FABP4 may play as a sensitive biomarker for valproate-induced metabolic dysfunction [7]. Interestingly, several studies have reported elevated FABP4 levels in pregnant women with pre-diabetes [8], and then in those pregnant women with pre-eclampsia developed later [9]. However, whether circulating FABP4 potentially predicts pre-malformation fetus in pregnant patient with epilepsy has not yet been investigated. Here, our report aimed to validate the proposed hypothesis from the present clinical data.

Clinical Study

Two participants were physically examined and clinically diagnosed for further data analyses. Blood samples were aseptically collected from the elbow vein. The plasma was collected by centrifugation at 5000rmp (room temperature)

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and immediately stored at -20°C for biochemical assays. In the current study, the participants signed the informed consent forms. This study was conducted according to protocols approved by the institutional ethical committee of Guigang City People's Hospital. In addition, the clinical study was performed as following the Ethical Guidelines of the Declaration of Helsinki [10].

Case Presentation

Circulating plasma was harvested from an epileptic pregnant woman (aged 21-year, gestation 18 weeks), and her fetus developed around 4-month old. Notably, FABP4 level (22.27 nmol/L) was two-fold lower in epileptic women whose pre-malformation fetus developed when compared to those in normal control (48.41 nmol/L). When seizure, epileptic patient was orally given with valproate monotherapy (400mg each time) between 2014/12 and 2017/05. In clinically biochemical diagnosis, abnormal conditions in epileptic patient were not detected in comparison with clinical references. As a result, pre-malformation fetus with possible organs retardation was screened using ultrasonic inspection, speculating sodium valproate-induced potential embryotoxicity over time **(Figure 1A)**. In validation, a real-time blood concentration of valproate was 71.61 μg/ml using high performance liquid chromatography (HPLC) assay. In a healthy pregnant woman (aged 27-year, gestation 16 weeks), the serological hormonal data showed normal levels of estradiol (456.5 pg/mL), progesterone (34.57 ng/mL), beta-human chorionic gonadotrophin (328.80 mIU/mL), and thyrotropin (1.64 μIU/mL), free thyroxine (11.92 pmol/L), free triiodothyronine (pmol/L), as well as alpha-fetoprotein (57.29 U/mL), implying that fetus develops healthily **(Figure 1B)**.

Discussion and Conclusion

In clinical practice, monotherapy can be effective and well-tolerated in adult patients with epilepsy [11-13], such as lacosamide, brivaracetam, eslicarbazepine acetate. However, the onset of anticonvulsant embryopathy, such as malformations or growth retardation, may be increased in infants when epileptic mother uses anticonvulsant drugs *in utero*. The pharmacological treatment of epilepsy during pregnancy represents a major clinical challenge since the potential adverse effects and teratogenic hazard of drugs should be balanced with the maternal and fetal risks related to poor seizure control. In these preliminary data, this may be a first report to assess maternal circulating FABP4 in connection with the development of pre-malformation fetus in epileptic pregnant patient. Thus, FABP4 biomolecule may play a key role in the development of fetal development. Further, it may be the perspective clinical observation to report circulating FABP4 in relation to the development of pre-malformation fetus in pregnant woman with epilepsy, and FABP4 is characterized with independently predicted pre-malformation fetus. In conclusion, this report demonstrates that circulating FABP4 functions

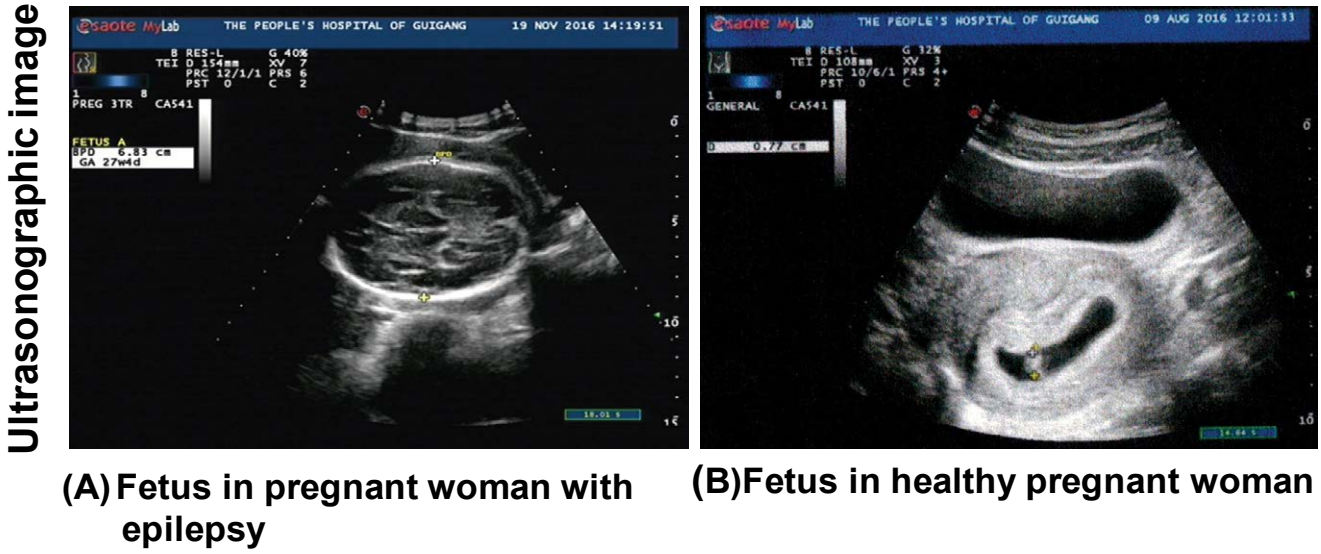

Figure 1: Case Presentation.

as a potential biomarker for prediction of malformation fetus in epileptic pregnant woman who exposed to valproate monotherapy.

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Declaration of Interest

The authors declare no conflicts of interest and are responsible for the contents of this study.

References

1. Sperling MR. The consequences of uncontrolled epilepsy. *CNS. Spectr* 9(1), 98-101 (2004).
2. Holmes LB, Harvey EA, Coull BA, *et al*. The teratogenicity of anticonvulsant drugs. *N. Engl. J. Med* 344(1), 1132-1138 (2001).
3. Smathers RL, Petersen DR. The human fatty acid-binding protein family: evolutionary divergences and functions. *Hum. Genomics* 5(1), 170-191 (2011).
4. Chmurzyńska A. The multigene family of fatty acid-binding proteins (FABPs): function, structure and polymorphism. *J. Appl. Genet* 47(1), 39-48 2006.
5. Bag S, Ramaiah S, Anbarasu A. fabp4 is central to eight obesity associated genes: a functional gene network-based polymorphic study. *J. Theor. Biol* 364(1), 344-354 (2015).
6. Furuhashi M, Saitoh S, Shimamoto K, et al.. Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological Insights and Potent Clinical Biomarker of Metabolic and Cardiovascular Diseases. *Clin. Med. Insights. Cardiol* 8(1), 23-33 (2015).
7. Li R, Liang L, Wu X, et al. Valproate acid (VPA)-induced dysmetabolic function in clinical and animal studies. *Clin. Chim. Acta* 468(1), 1-4 2017.
8. Ning H, Tao H, Weng Z, et al. Plasma fatty acid-binding protein 4 (FABP4) as a novel biomarker to predict gestational diabetes mellitus. *Acta. Diabetol* 53(1), 891-898 (2016).
9. Wotherspoon AC, Young IS, McCance DR, et al, Diabetes and Pre-eclampsia Intervention Trial (DAPIT) Study Group. Serum Fatty Acid Binding Protein 4 (FABP4) Predicts Pre-eclampsia in Women With Type 1 Diabetes. *Diabetes. Care* 39(1), 1827-1829 (2016).
10. Guo C, Pan Q, Su M, et al. Clinical immunophenotype of nasopharyngeal neuroendocrine carcinoma with metastatic liver cancer. *Clin. Chim. Acta* 471(1), 283-285 (2017).
11. Lattanzi S, Cagnetti C, Foschi N, et al. Lacosamide monotherapy for partial onset seizures. *Seizure* 27(1), 71-74 (2015).
12. Lattanzi S, Cagnetti C, Foschi N, et al. Brivaracetam add-on for refractory focal epilepsy: A systematic review and meta-analysis. *Neurology* 86(1), 1344-1352 (2016).
13. Lattanzi S, Cagnetti C, Foschi N, et al. Eslicarbazepine acetate as adjunctive treatment in partial-onset epilepsy. *Acta. Neurol. Scand* (2017).