Minireview Article

Valproic acid syndrome: a mini review

ABSTRACT

Aims: To provide a systematic review on the occurrence of valproic acid syndrome, to, among others, elucidate the characteristics of this syndrome.
Study design:A systematic review was performed.
Place and Duration of Study: Laboratory of Biomathematics of the Federal UINiversity of Alfenas, Minas Gerais State, Brazil, between June 2022 and July 2023.
Methodology:A systematic search of articles was performed using the CAPES Periodic plataform a searcher from the Education Ministry of Brazil that contains Web of Science, Scopus, MedLine and other bases, from 1984 to 2023. For this review, the subject's "syndrome of valproic acid", "valproic acid syndrome and toxicity", "valproic acid syndrome and malformations" were searched together using the type of material "articles" in English language. Some articles about "pregnancy's cares" were used for epistemological composition of this work content subjects as, for instance, "general toxicity" and "others (development; health care; …)".
Results: From the 1061 articles after the exclusion and the inclusion criteria made with the subjects most pertinent to the objectives of this work, added with the subjects "pregnancy cares" and "others"; 1005 articles were excluded, remaining 56 ones. Four of total from 56 texts were 4 about "general toxicity"; 19 about "others"; 4 about "Pregnancy cares" and 29 about "valproic acid".
Conclusion: The analysis of the articles studied in this work indicates that valproic acid is a teratogen that leads to a syndrome that receives its name in fetuses whose mothers use it as an antidepressant drug, causing several physical defects in general and behavioral defects due to the impairment of the neural system. In this sense, it is essential that the team caring for pregnant women know the history of the pregnant woman and check all the medications she is using and replace those with a teratogenic potential, especially if the patient has a diagnosis of mental illness such as depression.

Keywords: Valproic Acid Syndrome; Toxicity; Malformations; Valproic acid; Pregnancy cares.

1. INTRODUCTION

Healthy human embryonic development is a continuous action dependent on factors such as woman's age, hormones, maternal-fetus interactions [1] as the nutritional status of the mother [2], inter alia. The development has critical periods in relation to the health of the fetus, some of them occur in early pregnancy as the formation of the neural tube whose problems can be anencephaly, spina bifida, myelomeningocele [3], among other causes, these disorders could occur if some substances called teratogens are ingested by the mother.
Preventive medicine processes should provide pregnant women with indications on the care of the gestation phase, including on substances that may be harmful to the embryo/ fetus such as alcohol use [4], drugs and medicines that are part of the scope of various textbooks and institutions [5].
Prenatal care, described as an antepartum program with actions and risk assessments coordinated by the multidisciplinary team and with psychological support, aims to provide a comprehensive care to pregnant women, promoting a healthy preparation for pregnancy and ensuring a healthy development of their offspring. These activities are the responsibility of a multidisciplinary health team that must be attentive to the history of patients and follow the recommendations of the prevention of possible accidents with pregnant women [6] as the use of potentially teratogenic

substances, since part of congenital malformations originate at critical moments of the formation and the initial growth of embryonic structures [5].
The prenatal health care plan is ideally established from the diagnosis of pregnancy to the delivery, monitoring and meeting demands according to the gestational age, especially in developing countries [7].
If any ingestion of teratogenic substances occurs by the pregnant woman, the type of abnormality will depend on the class of drugs used, the development period, the dose.
The historical situation in relation to teratogens has as relevant the case of thalidomide, a medication prescribed in the 50s to control morning sickness in pregnant women who, tragically, culminated in thousands of children born with malformations, especially in the limbs, and some systemic repercussions, such as cardiac, renal and ocular disorders [8].
This history has led to the modification of drug release processes for use in humans and to the increase of care for potentially toxic substances in a global unification of care in relation to pharmacovigilance [9] mainly for pregnant women, therefore, cases of use of these substances by pregnant women who have contact with the health system should not happen.
Valproic acid is a drug used in the treatment of epilepsy and bipolar disorder, but that has adverse effects on the embryo/ fetus in the gestational period, with various mental and systemic disorders associated with it such as craniofacial abnormalities, and skeletal defects [10,11]. From this perspective, comparative studies on teratogenicity caused by antiepileptic drugs confirmed that valproic acid was associated with increased risks of congenital malformations, including neural tube defects and hypospadias [11,12,13].
The relative severity of birth defects is dependent on the dose of valproic acid to which the child was exposed [14], which can manifest neurodevelopmental deficits, assuming behaviors similar to the autism spectrum disorder [11], malformations such as spina bifida, orofacial changes, polydactyly, craniosynostosis, interatrial communication [10]; complications may occur at the delivery, and fetal growth restrictions [12,15].
The child shows lower developmental quotients (DQ) and intelligence quotients (IQ), which affects the expected school development with negative results in the adult and in the occupational life of these individuals [16].
According to the above, if the contamination of a fetus/embryo with valproic acid occurs in a pregnant woman who was attended by the public health system, it is reasonable to ask whether there was a failure of this system in terms of organization, lack of knowledge on the subject and ineffectiveness in prevention.
Students of the medical internship of a Federal University of Brazil attended a child with valproic acid syndrome who was born after his mother was attended by the public health system (SUS), which generated a basis for a debate on the use of valproic acid by pregnant women and it was observed that the knowledge about the effects of teratogens among students, teachers and health professionals is still insufficient. Therefore, the aim of this work was to provide a systematic review on the occurrence of valproic acid syndrome, to, among others, elucidate the characteristics of this syndrome.

2. MATERIAL AND METHODS

For the purpose of this review, the subjects “syndrome of valproic acid”, “valproic acid syndrome and toxicity”, “valproic acid syndrome and malformations” were searched together using the type of material “articles” in the English language. They were searched on the CAPES Periodic platform that contains Web of Science, Scopus, MedLine and other bases, from 1984 to 2023, to form the epistemological basis of the review in a total of 1061 articles. Some articles about “pregnancy’s cares” were used for epistemological composition of this work content subjects as, for instance, “general toxicity” and “others (development; health care; …)”. The set of subject content about valproic acid (“syndrome of valproic acid”, “valproic acid syndrome and toxicity”, “valproic acid syndrome and malformations”) was called in the table 1 (table 1) as just “valproic acid”.
Of these 1061 articles, those considered most suitable to the objective of the present review were used, i.e., those whose theme was associated with the valproic acid syndrome, malformations, and toxicity. The basis of scrutiny for choosing articles that dealt with similar subjects was the relevance of the subject to propose this work and the articles published in the last 5 years.

From this analysis and considering the themes closer to the objective, the exclusion criteria were duplicated within the subjects together with the papers about only pharmacological purposes and only about the clinical data on the valproic acid, and the less recent articles. However, some articles as the classic ones from 1984 were used because cited for the first time the valproic acid syndrome.

3. RESULTS AND DISCUSSION

From the 1061 articles after the exclusion and the inclusion criteria made with the subjects most pertinent to the objectives of this work, added with the subjects “pregnancy cares” and “others”, 1005 articles were excluded, remaining 56ones (table 1). Four of total from 56 texts were 4 about “general toxicity”; 19 about “others”; 4 about “Pregnancy cares” and 29 about “valproic acid” (table 1).

Table 1. Articles and its subjects studied in this work.

	References' numbers and texts	Subjects
1.	3. Cao R, Xie J, Zhang L. Abnormal methylation caused by folic acid deficiency in neural tube defects. Open Life Sci. 2022;17(1):1679-1688. doi:10.1515/biol-2022-0504	General toxicity
2.	4. Aversi-Ferreira TA, Nascimento GNL do. The effect of acute and chronic exposure to ethanol on the developing encephalon: a review. Rev Bras Saude Mater Infant. 2008Jul;8(3):241–9. Available from: https://doi.org/10.1590/S1519-38292008000300002.	General toxicity
3.	13. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. Curr Opin Neurol. 2019;32(2):246-252. doi:10.1097/WCO.0000000000000659	General toxicity
4.	45. Di Renzo F, Broccia ML, Giavini E, Menegola E. VPA-related axial skeletal defects and apoptosis: a proposed event cascade. Reprod Toxicol. 2010;29(1):106-112. doi:10.1016/j.reprotox.2009.10.004	General toxicity
5.	1. Hur C, Nanavaty V, Chehab AM, Yao M, Desai NR. P–212 Mitochondrial DNA content shows a significant association with timing of human embryo development and fertility diagnosis in euploid embryos. Human Reproduction. 2021, 36(1): deab130.211. https://doi.org/10.1093/humrep/deab130.211.	Others
6.	2. Anselem O, Goffinet F, Jarreau PH, Zeitlin J, Monier I. Perinatal survival among very preterm singletons born after detection of early-onset fetal growth restriction with or without maternal hypertensive disorders: A population-based study in France. Eur J Obstet Gynecol Reprod Biol. 2023;282:43-49. doi:10.1016/j.ejogrb.2023.01.004	Others
7.	5. Moore, KL. Embriologia Clínica. 11. ed. Publisher Guanabara Koogan S.A; 2021. Portuguese.	Others
8.	6. Brandão LD, Aversi-Ferreira TA. The experience of a nurse in the residency multidisciplinary deployed in Palmas-TO. Biosci. J. 2018 Mar. 26;34(2):486-94. Available from: https://seer.ufu.br/index.php/biosciencejournal/article/view/33421	Others
9.	8. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140-156. doi:10.1002/bdrc.21096	Others
10.	9. Hans M, Gupta SK. Comparative evaluation of pharmacovigilance regulation of the United States, United Kingdom, Canada, India and the need for global harmonized practices. Perspect Clin Res. 2018;9(4):170-174. doi:10.4103/picr.PICR_89_17	Others
11.	12. Mocquard C, Aillet S, Riffaud L. Recent advances in trigonocephaly. Neurochirurgie. 2019;65(5):246-251. doi:10.1016/j.neuchi.2019.09.014	Others
12.	14. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016;11(11):CD010224. Published 2016 Nov 7. doi:10.1002/14651858.CD010224.pub2.	Others
13.	16. Bromley R, Weston J, Adab N, et al. Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child. Cochrane Database Syst Rev. 2014;2014(10):CD010236. Published 2014 Oct 30. doi:10.1002/14651858.CD010236.pub2	Others
14.	17. Conselho Federal de Medicina (CFM – Brasil). Código de ética médica. Resolução nº 1.246/88. Tablóide, 1990. Portuguese.	Others
15.	18. Alyahya MS, Hijazi HH, Alolayyan MN, Ajayneh FJ, Khader YS, Al-Sheyab NA. The Association Between Cognitive Medical Errors and Their Contributing Organizational and Individual Factors. Risk Manag Healthc Policy. 2021;14:415-430. DOI: 10.2147/RMHP.S293110.	Others
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20.	30. Haseitel MA, Hardaman CG. Anticoncepción en mujeres epilépticas [Contraception in epileptic women]. Medicina (B Aires). 2021;81(1):62-68. Spanish.	Others
21.	31. Eléfant E, Hanin C, Cohen D. Pregnant women, prescription, and fetal risk, Editor(s): Anne Gallagher, Christine Bulteau, David Cohen, Jacques L. Michaud. Handbook of Clinical Neurology. 2020; 173:377.	Others
22.	46. Metruccio F, Palazzolo L, Di Renzo F, et al. Development of an adverse outcome pathway for cranio-facial malformations: A contribution from in silico simulations and in vitro data. Food Chem Toxicol. 2020;140:111303. doi:10.1016/j.fct.2020.111303.	Others
23.	48. Metruccio F, Battistoni M, Di Renzo F, Moretto A, Menegola E. Moderate alcohol consumption during pregnancy increases potency of two different drugs (the antifungal fluconazole and the antiepileptic valproate) in inducing craniofacial defects: prediction by the in vitro rat whole embryo culture. Archives of Toxicology. 2023;97(2):619-629. DOI:10.1007/s00204-022-03410-2.	Others
24.	24. Bedaso A, Adams J, Peng W, Sibbritt D. The relationship between social support and mental health problems during pregnancy: a systematic review and meta-analysis. Reprod Health. 2021; 18(1):162. DOI: 10.1186/s12978-021-01209-5.	Pregnancy cares
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56.	56. Doré M, San Juan AE, Frenette AJ, Williamson D. Clinical Importance of Monitoring Unbound Valproic Acid Concentration in Patients with Hypoalbuminemia. *Pharmacotherapy*. 2017 Aug;37(8):900-907. doi:10.1002/phar.1965	Valproic acid

According to the first article of chapter three of the Code of Medical Ethics, this professional is not allowed to cause harm to the patient, by action or omission, which may characterize malpractice, imprudence or negligence [17]. In this scope, the terms such as malpractice, imprudence or negligence may be caused by the fatigue of the practitioner in the daily activity and the common stress of the profession, however, in this case there may be a danger to the patient in a procedure or in a prescribed medication [18,19].

The various tables for the types of drugs with toxic potential can and should be consulted, but one cannot do it without the minimal technical knowledge for the correct treatment.

In this sense, a detailed anamnesis will allow the discovery of comorbidities if the analysis is well conducted [20] and aspects of humanized treatments with patients are considered [21], such as empathy, a fundamental behavior for a good health professional-patient relationship [22].

Neglect can be so serious that a real case can illustrate the situation. A pregnant woman warned the doctor that she was using valproate, however, the doctor insisted onkeeping using it. The patient showed knowledge that the drug could have been toxic, but the authority of the scullion was imposed on her to continue using it; as a consequence, her child has now Valproic Acid Syndrome.

Morphophysiological changes of the conceptus, embryo or fetus, are triggered at critical moments in pregnancy [5], also, therefore, the prenatal care requires a team of health professionals and psychological support [23,24] competent and committed to the maternal-fetal health to avoid cases such as the one mentioned.

It is necessary to consider, out of a necessary and pressing respect for women, that pregnancy is a time of many morphophysiological and emotional changes and it is natural that doubts about their body and their offspring arise. These anxieties should be known to the health team via prenatal consultations. Within these, the search for empathy between those involved in the pregnancy process becomes obvious.

The team must know the history of pregnant women and prevent any possibilities of problems with the woman and the fetus, including preventing the pregnant woman from using substances with toxic potential; in fact, it is necessary to establish an action plan from pregnancy with a constant monitoring [7], which will avoid, among others, teratogens of already well-defined causes [2]. Therefore, by implication, it is a doctor's duty to pay attention to the medications used before and during pregnancy, to the effects they may cause to the mother and her child, according to the stages of the embryonic/fetal development.

Valproate began to be used in the 1960s and 1970s for the treatment of bipolar disorder and epileptic seizures [25,26] as a GABA transaminase inhibitor [27], acting on partial and generalized seizures, and in bipolar mood manifestations [28]; nevertheless, its use during pregnancy has a teratogenic potential shown in a study of 7 children in 1984 [12.29,30] with effects similar to thalidomide [31], dose-dependent, but without a concentration that is safe for a human use [25], facts that have been observed since the 1980s.

However, only in 2017 European countries such as France and the United Kingdom, warned about the use of this drug during pregnancy [28].

In fact, using it in the first trimester of pregnancy increases the fetal risk of severe congenital malformations [32].

The teratogenic mechanism of the drug has not been fully elucidated; however, it is hypothesized to be related to an increased oxidative stress of the fetus antagonizing the effect of folate on the DNA synthesis [28]. Its main teratogenic mechanism is believed to be the inhibition of histone deacetylases that act on cell cycle and differentiation [33] and by inducingapoptosis in developing brain cells [34].

Valproate causes congenital malformations such as neural tube defects and hypospadias [12], neurodevelopmental and neurocognitive deficits [31,35,36], orofacial [25,37], musculoskeletal changes [38], cardiovascular changes [32,39]; complications at the delivery, fetal growth restriction [12,27,28].

After the birth, general and cognitive developments are compromised in children born to women with epilepsy exposed to valproate, comparatively [35], which compromises the educational level with consequent problems in the adult [16,25].

Studies with children exposed to valproate during the gestational period showed that the absolute risk of autism spectrum disorder (ASD) was significant (4.15%) [40], and experiments with murine models proved that the intrauterine exposure corroborated the development of problems similar to ASD [25,36,41,42,43], as the drug compromises morphologically the neuronal networks, the molecular markers, and reduces the number of Nissl neurons[44]; it generates musculoskeletal defects associated with a hyperacetylation of histones in somites (RENZO et al. 2010) via the inhibition of histone deacetylases with consequent abnormalities in gill arches due to problems in the gene expression regulated by retinoic acid [46,47,48].

Studies report that the offspring of pregnant rats taking valproate showed supernumerary and fused ribs and vertebrae [38,49], joints are smaller, fingers are proportionally long and overlapping, defects in the radius bone, deformities in the feet and in the rib cage [38].

Among the orofacial abnormalities, there may be a cleft lip and/or palate [48], epicanthic folds, a decreased nose size with anteverted nostrils, an elongated and flat lip filter, an altered cephalic index, craniosynostosis [42], a frontal protrusion, a wide nasal bridge, a bitemporal narrowing [50].

By inhibiting the histone deacetylase enzyme, disturbances in cardiovascular morphology occur [39], in fact, it is observed in Valproic Acid Syndrome, a hypoplastic aortic arch, an abnormal aortic valve, a coarctation of the aorta [42]and an interatrial communication [32]. Reports cited that a fetus exposed to valproate was born with a coronary arteriovenous fistula [50]and two other reports cited right pulmonary artery defects [51].

In lower animals, during the embryogenesis, studies with zebrafish exposed to valproate showed an enlargement of the pericardium, a pericardial edema with a consequent decrease in the blood circulation and due to an impaired cardiac function, some larvae did not survive [52].

The valproate is prescribed as anticonvulsant for seizure and bipolar disorders [53], however, it can, beyond the fetal disorders, to cause important problems in intoxication in adult, as hyperammonemia, anion gap acidosis, metabolic encephalopathy, and hepatotoxicity [54]. Specially in relation to Nervous Systemit induces cerebral edema [55] and the acetyl salicylic acid (AAS) increases the valproate level in the plasma[56].

Then, the importance of the care in to prescribe valproate is fundamental to avoid health problems bothin adults and pregnant, mainly.

4. CONCLUSION

The analysis of the articles studied in this work indicates that valproic acid is a teratogen that leads to a syndrome that receives its name in fetuses whose mothers use it as an antidepressant drug, causing several physical defects in general and behavioral defects due to the impairment of the neural system. In this sense, it is essential that the team caring for pregnant women know the history of the pregnant woman and check all the medications she is using and replace those with a teratogenic potential, especially if the patient has a diagnosis of mental illness such as depression.

Prevention is the main action to prevent children from presenting valproic acid syndrome with an emphasis on pregnant women. The actions of the multidisciplinary health team should be aimed at preventing the mother's behavior from affecting the embryos/fetuses in relation to their development.

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