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CASE REPORT

Cardiac dysfunction and prenatal exposure to venlafaxine

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Key Clinical Message

Venlofaxine, a widely used antidepressant, is known to cause a withdrawal syndrome. We present a case of neonatal transient ventricular dysfunction in a neonate exposed to venlafaxine in utero. Other causes of ventricular dysfunction were excluded. Neonatal ventricular dysfunction can be a possible side effect of maternal use of this drug.

Keywords

Cardiac dysfunction, newborn, pregnancy, serotonin reuptake inhibitors antidepressants, toxicity, withdrawal symptoms.

Introduction

Anxiety and mood disorders are frequent among the general adult population and during the reproductive years a significant proportion of women might experience depressive and anxiety disorders. The point prevalence for major and minor depression ranges from 8.5% to 11.0% during pregnancy [1].

In the overall population, including pregnant women, the most frequently prescribed drugs for treatment of these disorders are serotonin reuptake inhibitors (SRIs) antidepressants, in which are included selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine) and serotonin norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine [2].

It has been suggested that antenatal exposure to these agents can be associated with several neonatal symptoms, comprised under the designation of postnatal adaptation syndrome [3]. These symptoms include respiratory distress, diarrhea, emesis, feeding difficulties, hypoglycemia, hypothermia, jitteriness, tremor, irritability or agitation, hyperreflexia, hypotonia or hypertonia, excessive crying, sleep disturbances and seizures [2–9] and they have been specially reported after exposure to paroxetine, fluoxetine, and venlafaxine [3].

Since 2005, some studies have documented an increased risk for cardiac malformations in association to prenatal exposure to paroxetine, which were contradicted by recent published results [10, 11]. With respect to the recently introduced antidepressants like SNRIs, several published studies found similar outcomes to those described with the use of other antidepressant categories [3, 10–12]. However, it has been pointed that only a severe teratogenic effect could have been detected with the available data on these more recent antidepressants [12]. Noorlander et al. [13] observed that fluoxetine treatment during fetal development in mice could result in dilated cardiomyopathy, but in humans this was not reported previously. We describe a case of cardiac dysfunction in a neonate exposed to prenatal SNRIs in whom other possible causes were excluded.

Case History/Examination

A male term neonate was born to a mother who had been taking venlafaxine (75 mg/day) and alprazolam (0.5 mg/day) for treatment of depression and anxiety disorder,

throughout pregnancy. The mother had no other relevant medical history prior or during pregnancy. Family history was negative for congenital malformations or genetic disorders.

An obstetric ultrasound at 12 weeks showed an increased nuchal translucency. Amniocentesis at 16 weeks revealed a normal karyotype and a fetal echocardiogram was normal at 19 and 31 weeks of gestational age.

The baby was born at 39 + 5 weeks gestational, by vacuum-assisted delivery in the context of prolonged second stage of labor, with a birth weight of 3590 g (50th percentile) and an Apgar score of eight at the first minute and nine at the fifth minute. He was admitted to the Neonatal Intensive Care Unit at 24 hours of life with respiratory distress syndrome and feeding difficulties. Physical examination revealed tachypnea, costal retraction, tachycardia, hepatomegaly, and poor suction reflexes. There were no dismorphisms. Neurological examination was normal. Initial laboratory evaluation, including complete blood count, plasma electrolytes, C-reactive protein, glycemia, pH, plasma lactate, serum transaminases, serum creatine kinase and summary urine examination was normal. A blood culture was negative. A chest X-ray showed cardiomegaly and no lung changes. An echocardiogram in the second day of life documented dilatation of both ventricles with a left ventricular shortening fraction of 20% (normal reference value ≥29%) and mitral insufficiency. Persistent pulmonary hypertension of the neonate was ruled out.

Differential Diagnosis, Investigations and Treatment

Infectious, metabolic, endocrine, and genetic causes for cardiac dysfunction were excluded. Relevant results included negative blood polymerase chain reaction (PCR) for Epstein–Barr virus and Parvovirus B19; negative stool PCR for enterovirus; negative Cytomegalovirus culture from urine; negative serologies for Herpes simplex 1 and 2 and Human Herpes virus 6; negative newborn screening for inborn errors of metabolism (25 diseases screened) and normal thyroid function. A cerebral ultrasound scan was normal and the karyotype was normal with negative fluorescence in situ hybridization for chromosome 22.

Outcome and Follow-up

The newborn was started on regular furosemide and fluid restriction. Oxygen supplementation was discontinued after 2 days. Serial echocardiograms showed progressive improvement of cardiac function, with a normal left ventricle shortening fraction of 35% and normalization of left ventricular end diastolic diameter at 12 days of age. Feeding difficulties improved slowly and the newborn achieved full oral feeding at the end of the first month of life.

At 5 months of age, he was asymptomatic without medication and an echocardiogram showed good ventricular function, normal left ventricular end diastolic diameter, and no mitral insufficiency.

Discussion

Neonatal ventricular dysfunction is challenging. The etiology of dilated cardiomyopathy is found in only 30% of neonatal patients [14]. Most of those with an identifiable cause will have either a genetic syndrome or an inborn error of metabolism. Other identified etiologies are viral myocarditis, endocrine diseases, neuromuscular disorders, toxic agents, nutritional deficiencies, and ischemic disorders (coronary anomalies, prolonged arrhythmias). In the case reported, all these etiologies were discarded, namely the two major etiological groups. Neonatal metabolic screening in our country includes the most frequent inborn errors of metabolism related to cardiac dysfunction. Our patient had a transient but severe form of cardiac dysfunction, which is not usually associated with genetic syndromes or inborn errors of metabolism.

A possible role of serotonin in cardiac development and function has been identified and therefore a potential harmful effect of SRI antidepressants on fetal heart [15]. Although recent data do not demonstrate teratogenic properties of antidepressants in general, for SNRIs such as venlafaxine, the evidences on the level of risk are still numerically inconsistent and need to be clarified by further research. Three large prospective cohort studies [10–12] and three meta-analysis [3, 16, 17] that included the SNRI venlafaxine do not suggest an increased risk of congenital malformations, namely cardiac defects. In addition, a recent Nordic cohort study with emphasis on cardiac birth defects, reinforce these results [18]. On the other hand, a retrospective study suggests associations between periconceptional use of venlafaxine and some birth defects, including atrial septal defect and coarctation of the aorta [19]. In our patient, the concomitant presence of respiratory distress syndrome and feeding difficulties, as well as progressive improvement in cardiac function, suggesting acute and transitory rather than chronic or persistent damage to the myocardium, supports exposure to venlafaxine as a possible etiology in this context.

The mother was also taking alprazolam during the entire pregnancy and we could suspect that neonatal symptoms and cardiac dysfunction could be a result of this medication. Nevertheless, a meta-analysis about fetal safety of benzodiazepines published in 2011, which synthesized nine studies with over one million pregnancies,

concluded that these drugs do not appear to increase teratogenic risk in general nor cardiac dysfunction [20]. An interaction with combined effects between alprazolam and venlafaxine cannot be excluded. Published data are not consistent. One study found that the combination of SSRIs and benzodiazepines during pregnancy was associated with an elevated risk of congenital heart disease [21]. Another study showed that the combined use of benzodiazepines and SSRIs or venlafaxine during the first trimester did not increase the risk of birth defects [18].

On the other hand, it is debated whether some of SRIs adverse neonatal effects are caused by serotonin withdrawal or toxicity [4, 6–8]. The serotonin withdrawal syndrome (neonatal abstinence syndrome) onset is between 2 days to 1 month from birth and is characterized by sleep disturbances, neurological, gastrointestinal, motor, and somatic changes [4, 8]. Exposure to venlafaxine during the third trimester of pregnancy carries a risk of approximately 30% for neonatal withdrawal syndrome [22]. The serotonin toxicity syndrome begins in the first hours after birth and the most common symptoms are neurobehavioral changes and respiratory difficulties [4, 8]. Based on this chronological and clinical definition, our case seems to fit in the probable toxicity effect rather than withdrawal.

Neonates with SRI-related syndrome are usually kept on a quiet low light environment with small feedings and mother-infant skin-to-skin contact. Neonates with severe symptoms need more aggressive treatment such as anticonvulsant therapy, intravenous fluids, and respiratory support [2, 8]. Our case required oxygen therapy, fluid restriction, furosemide, and nasogastric tube feeding for some days.

Since the degree of maternal depression plays a significant role in child development, maintaining euthymic mood in the mother throughout pregnancy and preventing postpartum decompensation are important goals of treatment. In women who discontinue antidepressant treatment prior to conception, 68% experience a relapse during pregnancy [22]. Therefore, optimal treatment of maternal depression must remain a primary concern but potential risks of in utero exposure to antidepressant medications must be weighed against risks of untreated psychiatric illness [4, 6].

To reduce or prevent neonatal symptoms, it has been suggested to taper or discontinue SRIs approximately 2 weeks prior to the due date and resume after delivery [2, 4, 8]. Some authors have also proposed a 3-day clinical observation period for neonates exposed to SRIs during the last trimester of pregnancy [7, 22].

In conclusion, although there is no evidence of causality between prenatal exposure to venlafaxine and cardiac dysfunction in the newborn, in the case described, it seems to be the most probable cause, since other etiologies were ruled out. As published data on SNRIs effects in the fetus is still conflicting and inconsistent, we emphasize the importance of reporting the upcoming cases, in order to give more insight into the understanding of this complex entity.

Conflict of Interest

None declared.

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