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Neonatal gynecomastia complicated by morphine induced hyperprolactinemia

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Abstract
Neonatal gynecomastia is defined as "benign proliferation of glandular breast tissue". It is considered to be a physiological variant seen in approximately 70% of infants in the first few months. Hyperprolactinemia & neonatal gynecomastia may be caused by several physiological, pathological and even pharmacological conditions.
There are multiple drugs that cause an increase in the concentrations of serum prolactin such as antipsychotics, opioids (morphine) and so many more. We report a rare case of neonatal gynecomastia complicated by morphine with no similar cases are reported in humans. We are hoping by this case report we increase the awareness of the possible role of medications in inducing neonatal gynecomastia among pediatricians and neonatologists.

Keywords: neonatal gynecomastia, hyperprolactinemia, neonatal breast enlargement, neonatal mastauxe

Introduction
Neonatal gynecomastia is defined as the "benign proliferation of glandular breast tissue" [1]. It is considered to be a physiological variant between infants occurs in approximately 70% in the first few months after birth, the breast bud attains a diameter of 1 to 2 cm in this condition [2]. The exposure of the fetus to maternal hormones throughout pregnancy or during breast-feeding is thought to be the most logical cause of premature breast development. The drop in maternal estrogen levels in neonatal blood after birth triggers the secondary secretion of prolactin, an anterior pituitary hormone that initiates and maintains lactation, leading to physiological hyperprolactinemia and milk secretion known as Witch's milk in 5-20% of newborns [2, 3, 4].
Several physiological and pathological factors can lead to hyperprolactinemia. However pharmacological factors can also play a role, and several drugs such antipsychotics and opioids (morphine), are known to cause increase in serum prolactin [5, 6, 7].

Case Description
We describe the case of a 1-month-old Somali girl (full term with birth weight of 2.66kg) who was admitted to the pediatric intensive care unit for the treatment tetanus neonatorum. She was intubated and mechanically ventilated and was administrated midazolam, diazepam, pancuronium, phenobarbital and morphine infusion (15mcg/kg/hr).
Two weeks later, she started to develop bilateral breast swelling. An initial diagnosis of mastitis was made and she was administrated a 10 days course of antibiotics (cloxacillin). However the swelling did not improve. An ultrasound revealed bilateral heterogeneous structures within both breasts, that were larger and more prominent on the right side (approximately 3x2 cm). The lesions exhibited an echoic center with peripheral hypo-echoic components. Further mild internal vascularity, no significant skin thickening, and no drainable collection was noted. The patient was then referred to our endocrine team. On examination we noted bilateral engorgement, and breast buds that were 5cm and secreted milk on pressure. Dilated veins, no redness or hotness of skin, Tanner stage 3 breast development and prolactin levels of 2520 were also noted [see figure 1]

Fig 1

We diagnosed her with drug-induced (morphine) hyperprolactienemia, and we recommended that she gradually be weaned off morphine. We followed the patient closely. Her condition improved, and she was extubated. Further, the milk secretion had stopped, and the bilateral breast swelling had decreased. Her prolactin level was 2184 [see figure 2]

Fig 2

Discussion

Estrogen is a known cause of breast enlargement in 70% of newborns [3], and the prevalence of asymptomatic gynecomastia due to estrogen and androgen imbalance is 60%-90% in neonates [10]. In newborns, the exposure of the fetus to maternal hormones throughout pregnancy or during breast-feeding is thought to be the cause, and the production of maternal estrogen levels in neonatal blood decreases after birth leads to secondary secretion of prolactin [3, 4]. The most common differential diagnoses of breast swelling are premature thelarche, fibro-adenoma, and precocious puberty in girls and pubertal gynecomastia in males [11].

Several physiological, pathological and pharmacological cofactors can lead to hyperprolactinemia. Several drugs including opioids [5, 6], affect prolactin secretion; however, the underlying mechanism is not known. It is that opioids induce hyperprolactinemia by acting on the synchronization of the pulsatile pattern of prolactin or they may paly role in the stress-induced hyperprolactinemic response [5].

We report a rare case of neonatal gynecomastia complicated by morphine-induced hyperprolactinemia. No such cases have been reported in humans. We found two studies on animals. In one animal study, female rats were randomly divided into 4 groups and injected with either saline, morphine, morphine plus dextromethorphan, or dextromethorphan twice per day for 7 days. It was found that chronic administration of morphine induced higher prolactin concentrations as compared to the levels in control animals [8].

In the other animal study, researchers examined the effect of daily injections of morphine hydrochloride on galactorrhea in male cynomolgus monkeys. Nine monkeys were divided into 3 groups, and each group received subcutaneous injection of morphine (1.5, 3.0, or 6.0 mg/kg) daily for 74–130 days. The serum prolactin and testosterone levels were measured weekly 20 hours after the injection. The study found that morphine induced a transient rise in prolactin levels and a decrease in testosterone levels which can lead to spontaneous galactorrhea in male monkeys [9].

Conclusion

Although neonatal gynecomastia is thought to be a induced primarily by physiological factors, other factors, such as medications (opioids), could also induce or complicate this condition to a degree that might leads us to think of other possibilities like mastitis, precocious puberty, and prolactinoma.

Pediatricians and neonatologists should be aware of the possible role of medications in inducing neonatal gynecomastia.

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