Unexpected Systolic Murmur in an Extremely Low Birth Weight Infant Undergoing Insulin Therapy

Guglielmo Salvatori [1] *, Giulia Brindisi [2] *, Mario Colantonio [3] and Anna Maria Zicari [2]

1 Neonatal Intensive Care Unit and Human Milk Bank, Department of Neonatology, Bambino Gesù Children's Hospital, IRCSS, Rome, Italy
2 Pediatrics Department, Umberto I Hospital, Sapienza University, Rome Italy.
3 Departmentt of Neonatology, S.Camillo Forlanini Hospital, Rome Italy
* Contributed equally
***** Correspondence: **G**iulia Brindisi (giulia.brindisi@gmail.com)

Abstract

Background Hypertrophic cardiomyopathy (HCM) in newborns is a rare and pathological condition with heterogeneous etiologies. Among all the different causes of HCM, hyperinsulinism is not generally reported but the relationship between hyperinsulinism and cardiac hypertrophy (CH) is known.
Case presentation We report the case of cardiac hypertrophy (CH) in an Extremely Low Birth Weight (ELBW) infant who underwent insulin therapy after the onset of a persistent hyperglycemia due to parenteral nutrition (PN); the finding supports the hypothesis of a newborn's iatrogenic hyperinsulinemia in cardiac involvement. Despite the effects of hyperglycemia on myocardial cells are well known and infants of diabetic mother may develop cardiac malformations, the consequences of an early administration of insulin in preterm infants have never been fully clarified and are often underestimated. The present case underlines the importance of a close cardiological follow-up in infants undergoing insulin infusion for an alteration in the glucose metabolism PN-related, that is a common finding in preterm infants.
Conclusion: This case report, also considering the scientific literature, reiterates the importance of taking into account hyperinsulinism in the differential diagnosis of cardiac hypertrophy.

Keywords Hyperinsulinemia; Hypertrophic cardiomyopathy; Hyperglycemia; Parenteral Nutrition (PN), Extremely Low Birth Weight (ELBW).

Introduction

Hypertrophic cardiomyopathy (HCM) in newborns is a rare and pathological condition in which histological disruption of the myocardial structures creates a thickening of the heart muscle.[1]
HCM etiology is extremely heterogeneous, including malformation syndromes, inborn errors of metabolism, neuromuscular disorders even if most cases are due to mutations in cardiac sarcomere protein genes.[2]
Among all the different etiologies of HCM, hyperinsulinism is not generally reported but the relationship between hyperinsulinism and cardiac hypertrophy (CH) is known. In fact hyperinsulinism is mostly linked to CH rather than HCM, which requires histological and functional disaggregation's criteria. The real cause of CH is particularly important to understand, especially for its implications in clinical practice and for the prognostic and/or therapeutic consequences.[1]

CH is defined by echocardiographic diastolic septal thickness or diastolic left ventricular wall thickness equal to ≥ 2 standard deviations above the mean (Z-score ≥ 1.96; corrected for age, sex, and body size). [3,4,5]

In newborns and infants, the etiology of hyperinsulinism can be linked to many different causes: congenital hyperinsulinism (transient and persistent), maternal diabetes, insulin resistance syndromes, hyperinsulinism syndrome-related (such as Becwith-Wiedemann, Costello, Noonan and Leopard syndrome) and hyperinsulinism drug-related (excessive infusion of insulin).[1]

Considering only a few causes of hyperinsulinism among all those listed above, in neonates with **congenital hyperinsulinism**, fetal hyperinsulinemia increases the storage of glucose and lipids with a consequent hyperplasia and hypertrophy of myocardial cells. This is generally a transient phenomenon, secondary to stressfull condition, as the septal thickness progressively decreases to normality within the first months of life, generally without any complications, although in some cases beta-blockers are required.[6]

The persistent congenital hyperinsulinism, instead is due to a focal or diffuse overproduction of insulin originated by the pancreas in relation to various genetic disorders [6].

Also in **maternal diabetes**, hyperglycemia can produce fetal hyperinsulinemia that can persist till the neonatal period. Hyperglycemia is a known teratogen factor [7,8] and might result in a variety of cardiac defects in newborns. [9,10,11,12]

Even though, epidemiologic and prospective studies have shown that glycosylated hemoglobin A1c level, in the 6 months before conception and during the first trimester of pregnancy, correlates with the increased incidence of major malformations such as neural tube, cardiac defects and spontaneous abortions, the specific effects of hyperglycemia are still unclear. [13,14]

However gestational diabetes acts with a teratogen effect on the embryo, already from the first weeks of gestation, resulting in primary defects of cardiogenesis, related with to the deregulation of expression of genes coding for cardiac development. In the second trimester of gestational age, maternal hyperglycemia and the relative fetal hyperinsulinemia may exclusively cause asymmetric hypertrophic cardiomyopathy, with a thickening of the interventricular septum and lower posterior ventricular wall, which is usually associated with a biventricular dilatation and mitral regurgitation in mesosystolic phase.[15] In infants of diabetic mothers the incidence of congenital cardiac disease is about 3.6%, while this is 0.8% in the general population. [16]

In particular among the 30% of infants without congenital cardiac diseases born from diabetic mothers, the echocardiographic exam shows an interventricular septum and ventricular walls hypertrophy with a ratio from interventricular septal/ left posterior ventricle wall higher than 1,3. [17]

There are also cases of hyperinsulinemia secondary to an **excessive infusion of insulin**, as in the case report presented. A multicenter case-control study, conducted by Bearsall et al., showed that insulin infusion administered to hyperglycemic VLBW infants in the first weeks of life resulted in a significant gain of glucose and total energy intake but with an increased risk of hypoglycemia without providing a significant reduction of mortality and morbidity. [18]

Insulin has the role of an anabolic hormone and acts as a cardiac growth factor, promoting cardiac hypertrophy thanks to the interaction with its receptors on heart muscle cells. So CH related to a hyperinsulinemic condition is characterized by an exuberant growth of single myocardiocytes due to the anabolic insulin effecting the heart as a whole.. [1]

Moreover, many authors reported that in the majority of cases, cardiac hypertrophy due to a hyperinsulinemic condition is asymptomatic and also reversible after the normalization of insulin levels. [19,20,21,22]

For the differential diagnosis of hyperinsulinism in newborns see Table n1 below.

Tab n1. Differential diagnosis of hyperinsulinism in newborns

Disease	Hyperinsulinism type	Hyperinsulinism trigger cause/etiology
Transient Congenital hyperinsulinism	Transient	Maternal Stress
Persistent Congenital hyperinsulinism	Persistent	Genetic disorders that cause a focal or diffuse overproduction of insulin in the pancreas.
Maternal Diabetes	Transient	Maternal Diabetes
Hyperinsulinism syndrome-related (such as Becwith-Wiedemann, Costello, Noonan and Leopard syndrome)	Persistent	Syndromes and genetic disorders
Hyperinsulinism drug-related	Transient	Excessive infusion of insulin

Case presentation

We describe the case of a ELBW infant (25+1 weeks of gestational age, birth weight 880 grams, length 33 cm, cranial circumference 24 cm), born from a caesarean section due to a cervical insufficiency. The mother was a multiparous 27-year-old girl who had shown a shortening of the uterine cervix in the last month of pregnancy and started taking vasosoprexine isoxsuprine hydrochloride to reduce uterine contractions and the possible risk of a premature birth. An intravenous glucocorticoid bolo was administered only few hours before the delivery. The APGAR score was six , one minute after birth and after five minute the newborn underwent orotracheal intubation, surfactant administration and was mechanically ventilated for the following 96 hours. After extubation he was supported with nasal continuous positive air pressure (n-CPAP) and oxygen to maintain oxygen saturation between 90 and 95%. Moreover, the infant developed jaundice and underwent phototherapy until the fourth day of life.

After the first day of life, ibuprofen was started (10 mg/Kg, 4 mg/Kg, 4 Kg/mg to 24 hours apart), due to the presence of a patent ductus arteriosus and eritroprotein (250 units 3 times /week) for the subsequent anemia. No alterations of procalcitonin (PCT) and C-reactive protein (CRP) were detected in order to exclude diagnosis of sepsis. Moreover during hospitalization the child was not undergoing any steroid therapy. The evidence of feeding intolerance (gastric residuals, abdominal distension) required the start of full parenteral nutrition (FPT), but, after 3 days, a persistent hyperglycemia arose (217 mg%).

In order to control blood glucose and gain weight, a continuous insulin infusion was administered for ten days. The infusion rate was adjusted (from 0,1 UI/Kg to 0,01 UI/Kg) to obtain the stabilization of blood glucose levels that was reached after only six days from the beginning of insulin treatment. However, on the 15^{th} day of life, a systolic ejection murmur in mesocardium (2/6) was detected, and the infant developed an episode of desaturation during n-CPAP, requiring an echocardiographic exam and a doxapram hydrochloride infusion was started (0,5 mg/kg/h). Cardiac ultrasonography showed hypertrophic cardiomyopathy with severe thickness of the septum and free wall left ventricular (telediastolic diameter 4,7 mm), reduction of ventricular

cavity and velocity in ventricular outflow, right trabecular hypertrophy and mild mitral valve insufficiency. On the 17th day of life, electrocardiogram (ECG) showed an elevated ST segment, particularly in the left precordial leads. Subsequently insulin infusion was suspended.
The echocardiographic ultrasound exam, after 10 days from insulin suspension, showed a progressive reduction of free left wall septum and of trabecular hypertrophy.
After 40 days of life, the ECG was repeated showing a normal tracing and the ecocardioghraphic ultrasound revealed a further improvement in cardiac hypertrophy.
At the time of discharge the baby did not present retinopathy of prematurity (ROP), hypertension, renal failure, but outcomes of bronchodysplasia. At the age of 36 months was in good clinical condition.

Conclusion

The goal of nutrition for preterm infants should be to achieve a postnatal growth rate approximately equal to the rate of a normal fetus with the same gestational age. Unfortunately, most preterm infants, especially ELBW, are not fed sufficient amounts of nutrients to reach normal fetal growth rates.
The resulting extrauterine growth retardation is a significant problem that could result in short stature, organ growth failure, neuronal deficits with behavioral problems and low cognitive outcomes. [23,24]
This is the reason why it's very important to start adequate parental nutrition (PN) to avoid the possible serious consequences of inadequate nutrition for the needs of preterm infants.
In the first weeks of life, ELBW infants might present hyperglycemia in the range of 40-80 % of cases. [25]
Hyperglycemia among ELBW infants increases the risk of early death, intraventricular hemorrhage and extends the length of hospitalization, which suggests that prevention and treatment of hyperglycemia may improve the outcomes for these infants. [26,27]
Potential causes of hyperglycemia include sepsis, NEC, surgical treatments, infusion of vasoactive drugs and steroids, insulin resistance and/or relative insulin deficiency and high glucose intake, as in the case report described above. The standard approach to the management of hyperglycemia in infants involves the use of glucose restriction and/or continuous insulin infusion to achieve a normal level of glycemia and improve the nutritional uptake. [28,29]
This treatment can prevent osmotic diuresis, dehydration and electrolyte imbalance. In fact, the hyperosmolar state has been associated with an increased risk of intraventricular hemorrhage.However insulin infusion is not free from serious complications, including hypoglycemia that remains an important and risky possible consequence. [30]
To the best of our knowledge, the case reported, is the first case described in the literature of an ELBW newborn who shows a transient hyperinsulinemia after birth, due to **a iatrogenic intervention**, that might be responsible for cardiac complications, as documented by the close temporal relationship between the CH and the beginning, and then the suspension of insulin therapy.
Other cases described in literature, refer mainly to CH in presence of congenital hyperninsulinism or maternal diabetes. [16]
In this perspective, in the same way as many authors described cases of CH associated with gestational diabetes [31, 32] or congenital hyperninsulinism [33,22], the present case highlights the importance of a strict cardiologic follow-up in ELBW infants undergoing PN and subsequently insulin infusion.
In fact, the effect of insulin on myocardial cells is well known, even if most of the studies have been performed on rats.
Kruger M. et al. explained the association between cardiac hypertrophy and hyperninsulinism in diabetic rats, showing that high fetal insulin, decreases the expression of the N2B titin protein isoform in cardiac cells.[34]

The protein titin is the main mechanism for adjusting passive myocardial stiffness in perinatal heart development and also in chronic heart disease. Insulin controls the cardiac titin-isoform pattern by activating the phosphoinositol-3-kinase pathway.[34]
Therefore, insulin signaling, regulates both titin-isoform composition and titin phosphorylation, in embryonic cardiomyocytes and could contribute to an altered diastolic function in diabetic cardiomyopathy. [34]
Other authors suggested that chronic hyperinsulinemia in rats might increase body weight, tibia length, heart weight and left ventricular mass thanks to the anabolic function of this hormone. [35]
In other studies always conducted on animals, overfeeding is associated with left ventricular hypertrophy [36], because it increases the basal level of plasma insulin, leptin and the insulin/glucose ratio. [37]
On the other hand, in humans in particular, in obese patients with type-2 diabetes mellitus, the hyperinsulinemia in response to hyperglycemia, increases lipids content in myocardial cells. [38]
In addition, a recent review conducted by Paauw N.D. et al., emphasizes the role of insulin as a cardiac growth factor in hyperinsulinemic infants with CH. [1]
In fact, the heart is an important target for the anabolic effect of insulin that interacts with its receptors on cardiomyocytes, thus promoting cardiac hypertrophy. [39,40]
Moreover CH is found in many different hyperinsulinemic diseases, supporting the fact that CH develops regardless of the underlying cause of the high insulin levels. [1]
In this perspective, we speculate that the pathophysiology underlying cardiac hypertrophy in the infant described might be similar to the one assessed in hypertrophic cardiomyopathy of diabetic mothers' infants or in congenital hyperninsulinism. [41, 42,33, 22]
In conclusion, hyperinsulinism is linked to CH in many different hyperinsulinemic diseases and should be listed in the differential diagnosis of myocardial hypertrophy.
The interaction between insulin and its cardiac receptors can produce intracellular growth signals like a growth factor. So, the relationship between hyperinsulinemia and CH needs to be thought to provide the correct clinical practice and the best therapeutic strategies.
This is the first case described in the literature of an ELBW, in which a transient cardiac isolated condition, not associated with other pathologies, is due to an iatrogenic hyperinsulemia, and underlines the importance of a close follow-up in infants under insulin treatment, consequent to an altered glucose metabolism during PN.
However, the real and causal connection between insulin and CH in hyperinsulinemic conditions still needs to be clarified; in addition, other factors should be better evaluated since CH is not always found in all newborns with high insulin levels.
So, further studies are warranted to better define the potential consequences of the prolonged use of insulin therapy, and to clarify the cost-benefit relationship of this therapy in ELBW infants undergoing PN, for a period of their life.

Consent Written informed consent was obtained for the publication of this case report.

List of abbreviations: Nasal continuous positive air pressure (n-CPAP); Parenteral Nutrition (PN); Extremely Low Birth Weight (ELBW); Very Low Birth Weight (VLBW),; Electrocardiogram (ECG); Retinopathy of prematurity (ROP).

Authors' contribution GS and MC were involved in the patient's evaluation and clinical care. GS was involved in the conceptualization of the report, literature review, and manuscript preparation; GB was involved in supporting the writing of the original draft and in the review and editing fase.

A.M.Z was involved in the final revision of the manuscript and in supervision. All authors have read and approved the final manuscript.

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