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Congenital tuberculosis in an infant of a mother with relapsed multi-drug resistant tuberculosis: A Case report

DOI:<http://dx.doi.org/10.4314/njp.v49i3.8>

Accepted: 10th August 2022

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Abstract:

Although congenital tuberculosis (TB) is rare, it is associated with a high mortality rate. The infection is mainly acquired transplacentally and less frequently from infective lesions on the maternal genital tract. Many cases are missed in clinical practice due to the non-specific presentation of the disease hence the tendency to either miss the diagnosis or make the diagnosis late. We report an infant of a 32-year-old mother who was treated for multi-drug resistant TB before the index pregnancy and probably had a relapse during pregnancy. The

infant presented with features of sepsis at the age of ten days, but tuberculosis was only suspected when there was no clinical response to routine antibiotic therapy, and the medical history of the mother was reviewed. This report is to create awareness about the non-specific manifestations of the disease and highlight some helpful diagnostic methods in a resource-poor setting.

Keywords: Gene X-pert, Isoniazid monotherapy, Multi-Drug Resistant Tuberculosis, Neonatal sepsis, Neonatal Tuberculosis, Tuberculin Skin Test.

Introduction

Tuberculosis, a vaccine-preventable disease caused by *Mycobacterium tuberculosis*, has contributed to childhood mortality in Nigeria.^{1,2} The disease is known to affect children of any age outside the newborn period, and the burden in childhood has increased, particularly with co-infection with HIV.³ Tuberculosis is usually acquired from infected adults as children rarely infect each other. Therefore, a case of childhood tuberculosis indicates the disease's prevalence among the adult population. In 2014, childhood TB reportedly accounted for 6% of all national TB cases.⁴ The burden of TB in the general population has been worsened by the increasing trend of multi-drug resistance.⁵ Multi-drug resistance refers to the resistance of *Mycobacterium tuberculosis* to anti-TB drugs, including isoniazid and rifampicin.⁵ In Sagamu, using Gene-Xpert, rifampicin resistance was reported to occur in 10.7% of all confirmed TB cases, 16.5% among re-treatment cases and 3.5% among new cases.⁶ This disease is associated with more severe morbidities and higher mortality risk in TB cases. Therefore, this emergence necessitates a more stringent search for TB for prompt identification of Multi-Drug Resistant (MDR) cases to mitigate the impact of the disease.⁷

In the newborn period, TB may be congenital, when the tubercle bacilli spread to the foetus in utero or during passage through the birth canal or acquired when the bacilli spread from adult carers after birth. 8 Transmis-

sion of tuberculosis in the newborn may occur transplacentally. In this case, there will be a hepatic primary complex in the baby or aspiration of infected liquor during passage through the birth canal characterized by the presence of a primary complex in the lungs.⁹ When it occurs postnatally from ingestion of infected materials, the primary complex is usually located in the alimentary tract.⁹

This case highlights the challenges the non-specific clinical presentation of congenital TB poses to clinical management and contributes to the risk of neonatal mortality. This report aims to create awareness about this rare form of pneumonic disease in newborns and urge practitioners in maternity and neonatal health services to increase screening for TB as part of routine antenatal care services in resource-limited parts of the world, where TB is endemic.

Case Report

A 10-day-old male infant, one of a set of twins, was brought to the Emergency Room of the Olabisi Onabanjo University Teaching Hospital, Sagamu, on 24th October 2021, with complaints of sudden 'bluish' discoloration of the skin, loss of activity and breathlessness of two hours duration. He was recently breastfed and burped before laying him in the cot. There was no evidence of feed regurgitation or vomiting. He had no preceding or associated fever or cough. He was delivered

by spontaneous vertex method at approximately 34 weeks of gestation at a primary health centre following a week of spontaneous pre-labour rupture of foetal membranes. He reportedly cried immediately after birth, but both babies were hospitalized at the place of birth for four days for an unknown reason. The details of the perinatal events were not available. The birth weight was also unknown. The mother booked the pregnancy for antenatal care at the same primary health centre. She was hospitalized at the same centre for a febrile illness at the end of the first trimester (the diagnosis and treatment details were unknown). The twins were the first children in that marriage; the mother was a 32-year-old petty trader while the father was a 50-year-old sentry in the hospital. The babies were yet to be commenced on routine vaccination.

At presentation, the baby weighed 1.42kg, was acutely ill in severe respiratory distress, severely pale and centrally cyanosed with oxygen saturation of 34%, bradycardic with a heart rate of 64bpm, bradypnoeic (respiratory rate 28cpm) and hypothermic (35.2°C). There were no enlarged peripheral lymph nodes. The breath sounds were reduced in intensity with widespread coarse crepitations in all lung zones. Following resuscitation, the heart rate improved to 110bpm, but there were no cardiac murmurs. The abdomen was distended with tympanic percussion notes but no palpably enlarged organs. He was lethargic with generalized hypotonia and absent primitive reflexes. The external genitalia were rudimentary. The baby had several episodes of apnoea and was resuscitated until spontaneous respiration was achieved and sustained. The working diagnosis was prematurity with possible aspiration pneumonitis to exclude late-onset sepsis.

The random blood glucose was unrecordably low, and this was promptly corrected. The Packed Cell Volume was 53%, Total White cell count was $21.3 \times 10^3/\mu\text{L}$ with relative neutrophilia of 77.3%. The blood culture yielded *Staphylococcus aureus*, while the chest radiograph showed homogenous opacity in the right upper and middle zones with prominent air bronchogram, suggesting consolidation (Figure 1).

The baby was commenced on maintenance infusion with 8% Dextrose-in-5th Saline 160ml/kg/day, nasal bubble Continuous Positive Airway Pressure (CPAP) at 5cmH₂O, intravenous ceftazidime 100mg/kg/day and intramuscular gentamycin 5mg/kg/day, both in two divided doses. He had repeated episodes of hypoglycaemia despite dextrose infusion and expressed breastmilk feeding (brought from home by the father daily) until the third day of admission, when he achieved euglycemia and, after that, remained so. The baby remained tachypnoeic with fluctuating oxygen saturation levels (less than 90%) despite nasal bubble CPAP therapy and parenteral antibiotics for two weeks. Thereafter, the antibiotics were replaced with ceftriaxone and amikacin, according to the unit's protocol, due to poor response and inability to repeat the blood culture. On the

18th day of admission, the mother, who had not been available, visited and was noticed to have a chesty cough. On further interaction, she revealed she received care for TB at the hospital's Directly Observed Therapy (DOT) Clinic before the index pregnancy. This information was followed-up, and the DOT Clinic record confirmed she was managed for Multi-Drug Resistant TB, and the treatment was successfully completed. Tuberculin skin test and erythrocyte sedimentation rate were ordered, and the baby was commenced on isoniazid monotherapy, pending the outcome of investigations. On the 20th day of admission, the tuberculin skin test result showed an induration of 17mm. Therefore, a final diagnosis of Congenital TB due to suspected MDR-TB was made. While awaiting the institution of appropriate anti-TB therapy, the baby developed recurrent apnoea and eventually succumbed to the illness the same day. A post-mortem examination was not done as the parents did not consent to the procedure because of cultural disapproval. The mother and the other twin were referred to the DOT Clinic for further evaluation and management of the entire family.

Fig 1: Chest radiograph (anteroposterior view) of the baby showing diffuse opacities over the right upper and middle zones with prominent air bronchogram



Discussion

The highlights in the case described above include a preterm infant who had not been immunized against tuberculosis but presented for the first time with acute life-threatening events. The initial presumptive diagnosis was aspiration pneumonitis to exclude late-onset neonatal sepsis with radiological evidence of consolidation suggesting a form of pneumonia, hence the choice of broad-spectrum antibiotics therapy. Despite parenteral antibiotics and other supportive care, the baby remained critically ill until the mother was discovered to have a respiratory infection traced to her history of previous treatment for MDR-TB. The significantly reactive tuberculin skin test strongly supported the suspicion of congenital tuberculosis. However, the baby succumbed before further investigations such as gastric aspirate for Gene-Xpert could be performed.

Congenital acquisition of TB usually follows haematogenous spread from infected placental tissue and less commonly through spread from the maternal genital tract.¹⁰ The diagnostic criteria for the diagnosis of congenital TB, according to Cantwell (1994), include a demonstration of a primary complex in the infant's liver (or any evidence of tuberculosis within days after birth) and identification of *Mycobacterium tuberculosis* in the maternal genital tract or placenta.¹⁰ However, late presentation, difficulty in demonstrating the bacilli in the newborn, inability to examine the mother's genital tract for tubercular lesions and inability to perform a percutaneous liver biopsy in the infant are obvious limitations to the use of the Cantwell criteria in resource-poor settings. Therefore, there is a need for reliance on clinical parameters and ancillary investigations such as the chest radiograph, skin tuberculin test and erythrocyte sedimentation rate.⁸ Specifically, detailed maternal history, contact tracing of all adults and under-five children within her household, and multidisciplinary pre-natal management by the obstetrician, paediatrician and infectious disease experts would have played a significant preventive role.

Congenital TB is very rare. Unfortunately, clinical recognition of this infection is usually difficult; hence it is likely to be widely under-reported. The diagnosis could be missed as there may be limitations in investigative capability. The average age at presentation in the literature is 24 days though it may extend up to 84 days given the fact that the incubation period of the organism ranges from six to eight weeks.⁸ Interestingly, the index case presented as early as ten days, which agrees with a Taiwanese infant who also presented at the age of eight days.¹¹ The age at presentation may be as short as five days as reported in a Nigerian infant,¹² to as long as 28 days in an Indian infant,^{and 13} and 12 weeks as reported in another Nigerian infant.¹⁴ These other Nigerian reports emanated from Zaria, north-central Nigeria and Yenogoa, southern Nigeria. What is striking in the clinical presentation is the tendency to miss the diagnosis in the first instance,¹¹⁻¹³ since the features usually simulate sepsis, a more common clinical problem in early life. It is instructive that *Staphylococcus aureus* was isolated from the blood of the index case. This probably contributed to the delay in considering other possibilities when confronted with poor clinical response to antibiotic therapy. The usual combination of a third-generation cephalosporin and an aminoglycoside was deployed twice in the management of the infant to no avail. It was suspected that the organism isolated from the blood was a contaminant.

Nevertheless, it is more difficult in resource-poor settings where many mothers lack such records or do not access hospitals for maternity services. The diagnosis was facilitated in the index case because there was ready access to the mother's medical records in the same institution; otherwise, the diagnosis could have been missed. Therefore, accessing the medical records of mothers whose infants are critically ill is essential.

The index case presented with respiratory compromise, cyanosis, and abdominal distension in agreement with previous cases.¹¹⁻¹⁴ However, the absence of enlarged peripheral lymph nodes may not be surprising since the baby presented very early in life. Another Nigerian case that presented with enlarged lymph nodes in the literature was relatively older at presentation (twelve weeks).¹⁴ The lack of clinical responses to parenteral antibiotics and persistence of signs of severe illness such as tachypnoea, hypoglycaemia and oxygen desaturation suggested an 'unusual' diagnosis. In the index case, a reactive tuberculin skin test in an unvaccinated infant lent credence to the clinical suspicion of TB. Similar observations had been reported in the literature.^{12,14}

Reactive skin test strongly supports the clinical diagnosis since newborns ordinarily have low reactivity and poor T-helper responses.¹⁵ For resource-poor settings where diagnostic facilities may be non-existent, a tuberculin skin test may be helpful when congenital TB is suspected. The unusual clinical course in the infant aroused further clear suspicions when the mother was found to have completed the treatment for MDR-TB before the index pregnancy. Therefore, hers was probably a case of relapsed TB. TB relapse is common in pregnancy due to immunosuppression and also more likely with drug-resistant disease.^{6,16} This might be the first case of congenital TB from MDR-TB disease in the Nigerian literature. It is attractive to suggest that women of reproductive age should be put under surveillance after receiving treatment for MDR-TB, and attention should be paid to their reproductive profile so that they can be more closely monitored for likely relapse when pregnant. If the mother of the index case had been detected as soon as she relapsed and had received appropriate treatment during pregnancy, the foetuses might have been protected from infection with *Mycobacterium tuberculosis*.

Conclusion

In conclusion, it is essential to note that the burden of childhood TB has worsened with the addition of MDR to the spectrum of the disease among the adult population. Therefore, critically ill newborn infants receiving treatment for suspected sepsis but responding poorly to the usual regimen of antibiotics should be screened for possible TB. Surveillance for TB should be instituted among women of childbearing age, particularly during pregnancy.

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Non cardiac central cyanosis in the newborn: A case report of persistent pulmonary hypertension of newborn (PPHN) and review of literature

DOI:<http://dx.doi.org/10.4314/njp.v49i3.9>

Accepted: 29th August 2022

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Abstract: PPHN is a fatal neonatal emergency resulting from poor respiratory transition to extra uterine life, in spite of several advances in the management thereof.

It is an uncommon disorder characterized by persistence of fetal circulation seen in about 1 - 5 per 1000 live birth. Advances in the management includes, inhaled nitric oxide (iNO) and extra corporeal membrane oxygenation (ECMO) as gold standard. However a third of patients will not respond to standard treatment, coupled with its dearth in some developing countries as Nigeria.

In recent studies, treatment with oral Sildenafil; a phosphodiesterase inhibitor type 5 (PDE5) showed reduction in pulmonary

vascular resistance. This results in significant increase in oxygenation and a reduction in mortality without adverse effects. We report this uncommon case of one mo. old boy with PPHN who was seen in April 2019 at University of Nigeria Teaching Hospital Enugu. His clinical presentation, CXR and 2D Echo finding confirmed the diagnosis of PPHN. He was successfully managed with oral Sildenafil and Oxygen therapy. We recommend Sildenafil may be used as first-line treatment in settings where iNO, High Frequency Ventilation (HFV), and ECMO are unavailable.

Key words: Pulmonary hypertension, Newborn, Sildenafil.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a rare disorder of neonates.¹⁻⁴

An elevated pulmonary vascular resistance is required for an effective fetal circulation; however, if this persists after birth, pulmonary to systemic shunting occurs through persisting fetal channels (e.g. ductus arteriosus), thereby blood bypasses the lungs resulting in systemic arterial hypoxaemia.^{3,4} We present a case of this rare disorder in Enugu that was managed successfully with oral Sildenafil. There is no reported case in literature of PPHN in our environment

Case Report

He is CC, a 1 mo old male child who presented in April 18th 2019, with fast breathing and bluish discoloration that was noted few days after birth. The bluish discoloration is present all the time.

There is no known exposure to radiation, alcohol, indomethacin, aspirin or selective serotonin reuptake inhibitors (SSRIs) in utero. These drugs are implicated in pulmonary vasoconstriction. Labour was at term lasted for 6 hours and child did not cry immediately after birth. He

is the 4th in a monogamous nonconsanguineous marriage with four children two girls and 2 & 2 . Mother is 40 years while the father is 42years. There is no family history of cardiac defect or adverse cardiovascular event.

On examination: He was acutely ill looking. He had central cyanosis SaO₂ of 87% in room air. He was afebrile and a normal temp. 37.0 ° Anthropometry were normal for age; with weight of 4.5kg, length of 57 cm.

He had Respiratory rate of 60bpm, Pulse rate of 140bpm. Apex beat was displaced to the 5th LICS AAL, HS = S1 + S2 with loud P2 and splitting of S2. Non tender hepatomegaly. Normal tone and reflexes in all the limbs. CXR showed cardiomegaly. (Figure 1) 2D Echo showed RVH with RV dominance, mild tricuspid regurgitation (TR) with a shunting patent foramen ovale (PFO), with no other cardiac shunt. (Figure 2)

A diagnosis of PPHN was made and he was started INO therapy at 5ml/l, Tab Sildenafil 10mg tids, Tab frusemide 5mg bd, Tab Enalapril 0.625mg daily for 2weeks. He made marked improvement, as saturation improved to 97% in room air and establishment of normal respiration. He was on follow up at the Cardiology clinic for 3 months, with no adverse event or return of symptoms and was discharged

Fig 1: CXR: Showing cardiomegaly with hyperinflation

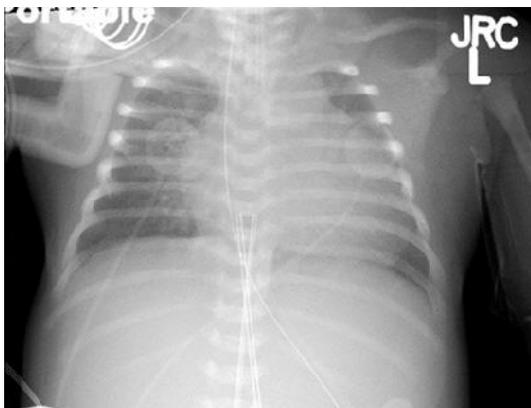
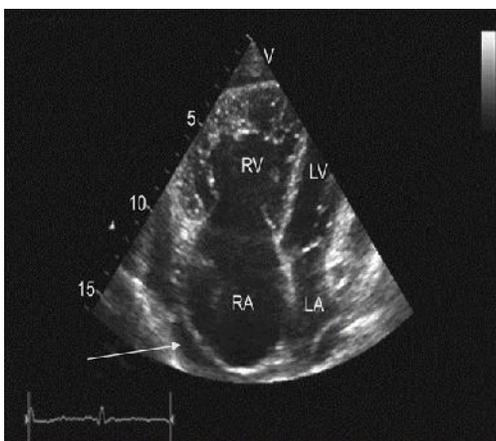


Fig 2: 2D Echo showed RVH with RV dominance and Moderate TR with RVSP = 45mmHg + RAP. Moderate PAP = 55mmHg, Shunting PFO and mild pericardial effusion



Discussion

Persistent pulmonary hypertension of the newborn (PPHN) is a rare disorder of neonates. It is the persistent of fetal circulation and occurs in 1:1500 live births worldwide. Authors are not aware of any reported case of PPHN in our study environment.

An elevated pulmonary vascular resistance is required for an effective fetal circulation; however, if this persists after birth, pulmonary to systemic shunting occurs through persisting fetal channels (e.g. ductus arteriosus), thereby blood bypasses the lungs and resulting in systemic arterial hypoxaemia.^{4,5} This is shown in figure 1 and 2 as hyperinflation with cardiomegaly and RV dominance with mild TR.

In utero pathophysiologically, increased pulmonary resistance is maintained by fluid-filled lungs, decreased nitric oxide (NO) and prostacyclin (PGI₂), and increased endothelin-1 (ET-1), And also products of the prostaglandin pathway, such as thromboxane and Serotonin^{3, 6-8}

PPHN is a transient event, which can be fatal without intensive and delicate neonatal management, to balanced ventilatory support and maintain low PCO₂, high PO₂ and pulmonary vasodilation.³⁻⁵ The aim of treatment is selective pulmonary vasodilatation and the following methods are used based on the context of feasibility.

Ventilation strategies using ECMO & High-frequency oscillatory ventilation (HFOV)

or use of pulmonary vasodilators such as Magnesium sulfate, Sildenafil, Bosentan, and Inhaled nitric oxide (iNO).^{5, 6, 8} Although iNO and ECMO are the gold standards^{8, 9} they are expensive modalities associated with technical difficulties in developing countries.^{4, 5} Also up to 50-60% of newborn fail to respond to it. Hence there is need for effective therapies, to stabilize this newborn in our environment.

PPHN first reported in 1969 by Gersony et al.^{1, 2} as persistence of fetal circulation in the absence of disease of the heart. Recently, sildenafil have helped shorten the course of this disease and reduce the mortality in these patients.^{5, 7, 9}

The optimal dose of oral Sildenafil in children is a range of 0.5 - 2mg/kg/dose every 6 hours.^{5, 7} Dosing is more frequent due to its short half-life. The patient received 1mg/kg 6 hourly with resolution of symptoms. Clinical indicators of a successful response were improved oxygenation indices with normalization in SaO₂ and stable vital signs.

The onset of action of Sildenafil varies from 20 minutes to 3 hours after oral administration. The consensus on duration of treatment is not well defined. The favored approach is to observe the individual response and stop medication after a clear response and to stop treatment after 6 - 8 doses without response.^{5, 7, 9}

Dosage reduction or cessation of treatment is advised following side effects eg hypotension. Other side effect of Sildenafil includes retinopathy of prematurity.^{5, 7, 9} An animal study showed that with improvement of pulmonary vascular resistance (PVR), there is associated systemic vasodilatation and deterioration of oxygenation when Sildenafil was administered with iNO.⁹ There is need for caution when both are concurrently used.

The differential of PPHN is Idiopathic pulmonary arterial Hypertension (IPAH).

This resolves later than PPHN. Alveolar Capillary Dysplasia with misalignment of pulmonary veins. (ACD-MPV) This is a rare uniformly fatal disorder of neonates, in which there is misalignment between the pulmonary capillaries. It is refractory to therapy. Others include primary isolated parenchymal lung disease; (Pneumonia, transient tachypnea of the newborn, respiratory distress syndrome)^{3, 5, 7, 9} These are differentiated by clinical setting and chest radiography. 2D Echo confirms the diagnosis of PPHN.

We conclude that in PPHN, administration of Sildenafil was an effective treatment associated with an increase in the oxygenation and a reduction in mortality with no

side effects. We recommend Sildenafil as first-line treatment in settings where i NO and ECMO are unavailable.

Authors' Contribution

Arodiwe IO initiated the case report, did the literature search and wrote the manuscript and with the other authors, Chinawa JN and Ujunwa FA did reviewed the manuscript for intellectual content and final approval of the version to be published.

Conflict of interest: None

Funding: None

Acknowledgment

We thank the head of Cardiology firm; Dr Obidike EO, Professor of Paediatrics for his mentorship.

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