Somato Publications ISSN: 2688-1071

Archives of Clinical Case Reports

Case Report

Improved Outcome of Pregnancy of A Case of Liddle Syndrome When Treated With Amiloride

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Received: 21 November 2019; Accepted: 23 January 2020; Published: 24 January 2020

Citation of this article: Mansouri, AH. (2020) Lessons Improved Outcome of a Case of Liddle Syndrome With Pregnancy When Treatment With Amiloride. Arch Clin Case Rep, 3(1): 05-08.

Abstract

Preeclampsia is a common complication with pregnancy,other genetic inherited hypertensive disorders are not. Few cases of Liddle Syndrome with pregnancy had been reported previously. Obstetric outcomewas commonly complicated by preeclampsia and fetal growth restriction (FGR) in the reported cases. This case had severe preeclampsia in the second pregnancy with alive baby followed by 2 intrauterine fetal deaths (IUFDs) both were severely growth restricted &the last one with also anhydramnios, hypertension and hypokalemia but not preeclampsia. When the diagnosis of Liddle syndrome was made & treated with amiloride she had a successful outcome of 1200 gm baby at 31 weeks who was delivered prematurely because of abnormal fetal heart rate test. The baby is alive and well at age of 10 months albeit small.

Background

Liddle Syndrome is a rare autosomal dominant condition caused by a point mutation of epithelial sodium channel (ENaC) encoding gene. This leads to increased function and hence sodium reabsorption & in most cases potassium secretion [1].

The resulting elevated blood pressure and low serum potassium concentrations suppress the renin-angiotensin-aldosterone system, resulting in hyporeninemia [2]. It is best treated withamiloride ortriamterene,both are diuretics that work by blocking the activity of ENaC, while spironolactone which is a mineralocorticoid receptor antagonists is ineffective at lowering blood pressure.

The pathophysiology of Liddle Syndrome was suggested to be due to a transport defect since 1991 [3]. Since then only few cases of Liddle syndrome with pregnancy had been reported worldwide [4,5,6]. Most of the reported cases had been complicated with fetal growth restriction (FGR) of the index pregnancy & only a few had reported previous pregnancies outcomes. This case was undiagnosed severe hypertension with hypokalemia first discovered in pregnancy with a significant unfavorable obstetric history which improved after treatment with amiloride.

The case

A 35 years old G 6 P 4+1 was referredby the medical specialist to the Obstetric clinic as a case of Liddle Syndrome for follow up (FUP)of her pregnancy.She was 15 weeks pregnant by a sure last menstrual period date. At presentation she had no complaints. She was on aspirin, folic acid, nifedipine, methyl dopa & amiloride.

Her first pregnancy was a first trimester loss, followed by a full-

term pregnancy delivered normally & she is not aware of any complication.

The third pregnancy was complicated by severe preeclampsia at term & she was delivered by Cesarean section (CS). The baby is alive & well.

The 4th pregnancy was complicated by severe preeclampsia at 24 weeks and an intrauterine fetal death (IUFD), she was delivered by CS for a previous CS & severe preeclampsia. All these pregnancies were managed in another hospital.

Four years ago, she presented to our hospital at 26 weeks of her fifth pregnancy with high blood pressure & severe hypokalemia, FGR (21-22 weeks on US), severe oligohydramnios. She was referred to the nephrologist, investigated & treated for the high BP & hypokalemia. In hospital the pregnancy was complicated by an IUFD. She was induced with half dose misoprostol & successfully delivered 500 gm baby with no complication. Before discharge,the results of investigations suggested a diagnosis of Liddle Syndrome.

Past History

She had the previous two Cesarean sections.

She was diagnosed as Liddle syndrome following investigation of persistent non-responsive hypokalemia & young age onset hypertension. As genome Exome sequencing to detect the gene mutation encoding for LS gene abnormality is not available in the hospital, the diagnosis was based on the low renin concentration, normal serum aldosterone, non- elevated urine potassium & elevated serum bicarbonate, plus the clinical history of high blood pressure & persistent hypokalemia not responding to spironolactone & a family history of hypertension & electrolyte abnormalities. She was advised to do the test in private laboratory, but she could not afford it.

Family History

Her father had hypertension & low potassium & died at age 52 with a heart attack.

Grandfather died with chronic renal disease.She had 3 sisters each had a pregnancy loss as an IUFD, but she does not know the cause.

On examination

- BP 153/82, Urine dipstick: Negative for proteinuria
- General examination: Within normal
- Per Abdomen: 16 weeks size pregnant uterus .Thefetal heart was positive by doppler.
- No lower limb edema.
- Serum Potassium was 3 mMol/L, the other electrolytes were normal
- A renew visit to the nephrologist was made.
- Maternal fetal Medicine (MFM) ultrasound (US) confirmed dates & a normal detailed anatomy.

She was advised to continue her medication & FUP every 2 weeks for both obstetric & medical obstetric specialist clinics.

The second visit, two weeks later, she was diagnosed to have gestational diabetes (GDM).She was referred to a dietician & a medical specialist for control of GDM.

She was followed up closely. Her BP & serum potassium were maintained.Her blood glucose was controlled by diet only. Serial MFM US confirmed accepted borderline fetal growth and normal amniotic fluid volume (AFV).

At 29 weeks of her pregnancy, she presented to theemergency room (ER) with elevated BP, proteinuria& upper respiratory tract infection (URTI) symptoms. Investigations for Preeclampsia: revealed normal Hemoglobin, platelets, coagulation profile, liver function tests (LFT)&a positive urinalysis for protein +2. Serum potassium was 3.4 mMol /L. She was admitted to the hospital with a diagnosis of superimposed Preeclampsiawithout severe features.

Course in Hospital

Further investigations revealed: 24 hours urine protein was 1.3 g/L and a normal creatinine clearance. There was increased urine micro-albuminuria, while urinary potassium was normal.

She was on preeclampsia protocol: BP, pulse & fetal heart check-up q 4h when awake, urine dipstick daily and q3 days preeclampsia work up.

Fetal monitoring included: daily NST, weekly biophysical profile (BPP)

MFM scan revealed acceptable fetal growth, normal AFV, normal Doppler velocimetry. A decision was made to manage conservatively unless severe features developed. A 48-hour course of Dexamethasone was given.During hospital stay the blood pressure was in the mild range 130-150 systolic/80-90 diastolic,on three antihypertensive medications (methyl dopa, amiloride, & nifedipine)

Two weeks after admission, MFM US revealed: poor interval growth (134 g over 2 weeks) at 4th percentile. Umbilical artery doppler showed increased resistance (RI): 0.8, middle cerebral artery pulsatiliy index(MCA PI): 1.5 indicating brain sparing,

AFV was normal& biophysical profile (BPP) scored 8/8. Non-stress test (NST) was reactive. She was planned for continuing vigilant fetal & maternal monitoring unless evidence of fetal jeopardy or severe features of preeclampsia.

A few days later,she was 31 weeks plus 3 days, her BP increased to 168/91& the NSTtracing was showing variable decelerations.She was taken for emergency Cesarean Section. She had a baby girl with a Birth weight of 1200 g, Apgar Score was 7, 8, 8 at 1, 5, 10 min. The baby was transferred to NICU,did well & discharged home on the 25th day of age.

The post operative period of the mother was uneventful. BP was in the range of 125-135 systolic /80-85 diastolic, methyl dopa & nifedipine were discontinued and she was maintained on amiloride. She was required to have correction of the hypokalemia by intravenous KCL & was kept afterwards on maintenance oral supplements. She was discharged home on the 7th postoperative day.She was seen in Gynecology clinic at her routine post CS visit & was advised for LARC contraception.

She was seen again with her baby girl at 4 & 10 months, she was well & healthy but underweight (5.6 kg.).

Discussion

The genetic abnormality of Liddle Syndrome is due to mutations in the genes on chromosome 16p12 that encode the beta and gamma subunits of the collecting tubule sodium channel (SCNN1B and SCNN1G) [7]. The result isinability to bind to (Nedd4) that normally removes the luminal sodium channel from the cell surface. That will lead to a "gain-of-function" which mimics the effects of hyperaldosteronism [8,9].

This case did not have the genetic study to confirm the diagnosis, but it was strongly suggested on clinical grounds. She had early onset hypertension & severe hypokalemia not responsive to spironolactone. She also had low renin concentration & normal serum aldosterone. She responded well to amiloride. Genetic studies are commonly not available commercially in developing countries & where it is available it is usually expensive & unaffordable. That's probably was the reason for relying on clinical diagnosis as others similarly also reported [10].

Interestingly her first pregnancy was not complicated by hypertension or preeclampsia. That could be due late onset of expression of the disease. It had been reported that even within Liddle syndrome kindreds, the age of onset is variable between & within family groups [11]. Also, some patients might not present with hypertension as had been shown in the systematic review that only 92.3 % of reported cases of Liddle's syndrome mutationspresent with hypertension [1].

Her other previous pregnancies were complicated by recurrent early onset severe preeclampsia which was worsening during subsequent pregnancies with earlier gestational age at onset. Two of her previous pregnancies were complicated by intra-uterine fetal deaths. The last pregnancy was complicated with severe growth restriction & oligohydramnios before the sudden IUFD.

Following the diagnosis and proper treatment with amiloride & other antihypertensive drugs, she carried the current pregnancy to 31 weeks plus 3 days & then she was delivered because of fetal heart rate abnormalities of a growth restricted fetus.

The outcome was a growth restricted but not hypoxemic baby girl of 1200 g. birth weight & normal Apgar Score. She did well & she was seen at age 11 months well but small.

The use of amiloride is recommended for LS patients especially when hypokalemiais significant. Although classified as in the Category B of teratogenicity,its safety in pregnancy cannot be tested in randomized controlled trials (RCTs), nor in cohort studies because only few conditions require treatment by amiloride during pregnancy.

Our patient failed to respond to spironolactone, apotassium sparing diuretic that competitively inhibits mineralocorticoid receptors in the convoluted tubules to promote sodium & water excretion & K retention [12]. Spironolactone is the initial standard treatment of hypokalemia.The lack of response to spironolactone supported the diagnosis of LS as the mechanism of K loss is not aldosterone dependent.

The association between preeclampsia & hypertension had been always described although a cause & effect was not yet established. A common pathophysiology had recently been suggested. A suggestion was made that that preeclampsia could be a variant of LS [13]. In that study,preeclampsia patients did not respond tohigh salt intake by decrease in plasma renin in contrast to a significant decrease in healthy pregnant or non-pregnant women. The explanation was that the renin-angiotensin-aldosterone is already suppressed.This suppression could be due to the ab-

errantly filtered plasma protease plasminwhich may activate the ENaCin the renal collecting ducts [13].

To our knowledge, this is the first case of improved perinatal outcome in the same patient when the pregnancy was treated with amiloride.

Conclusion

Recurrent Hypertension in pregnancy with superimposed severe preeclampsia would suggest a possibility & hence work up of genetic causes of secondary hypertension. The obstetric outcome presents with different clinical manifestations including placental insufficiency, FGR, preeclampsia & abruptio placentae. The use of the usual antihypertensives might not be enough to improve the outcome, Specific treatment depending on pathophysiology will probably do.

This report supports that early diagnosis of the cause of hypertension and appropriate medical treatment improved the obstetric outcome.

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