2021 RANZCOG Virtual Annual Scientific Meeting 15–18 February

Transient Leukaemia of Down Syndrome

An Important Differential For Foetuses Presenting With Hydrops Fetalis

Our case involves a 32yo G2P1 referred to WCH MFM department for second opinion and management of fetal hydrops at 27+5 weeks.

Pregnancy management prior to referral:

- High suspicion of Down Syndrome based on 1:6 risk Trisomy 21 on combined first trimester screen and high risk NIPT. Invasive testing declined.
- Bilateral mild renal pelvis dilatation, with otherwise normal anatomy and growth on morphology ultrasound.
- No structural cardiac defects identified on 24+ week fetal echocardiogram.
- Fetal hydrops identified at 27+ week growth ultrasound

Urgent after-hours review conducted:

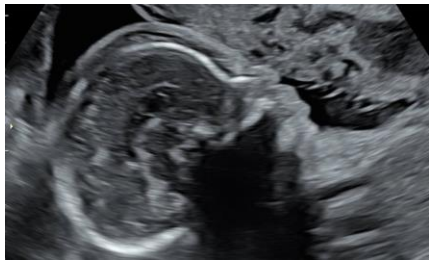
- Fetal hydrops with scalp/skin oedema, pleural effusions and mild rim ascites. Enlarged oedematous placenta
- Fetal heart assessed by cardiologist – normal rate and function with no evidence of structural abnormality or tricuspid regurgitation
- AFI 15, Umbilical PI >99%, MCA PSV 1.38 MoM, suppressed A-wave in DV.
- Maternal investigations including EUC/LFT, Group and Ab screen, TFT, Infection screen all negative

Ongoing management:

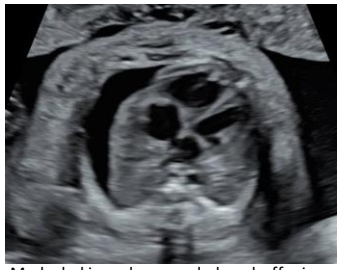
- Patient counselled regarding fetal hydrops and possible causes.
- Steroid loading commenced.
- Decision made for fetal blood sampling to allow for karyotyping, testing for anaemia and blood film analysis.
    - Performed at 28+ weeks – fetal Hb 120 with 15ml blood transfused
- FISH results confirmed diagnosis of Trisomy 21 and blood film consistent with myeloblastic proliferative condition
- Fetal LFTs abnormal, possibly reflective of myeloproliferative condition or fetal "stress" state/back "pressure" on liver.
- MDT discussion involving Family, Neonatal and MFM teams regarding diagnosis, prognosis, natural history and management options.
    - Decision made for active management with priority on meeting baby alive and providing best chance for care and survival
- LSCS performed at 28+1 weeks gestation – breech extraction complicated by 2.7L PPH due to very large vascular plexus over lower uterine segment.
    - 1390g male infant, with Apgars 5 and 7, Art pH 7.248, Ven pH 7.381 lactate 1.9
- Postnatal course complicated by symptomatic anaemia managed with pRBC transfusion and iron infusion, and endometritis treated with oral antibiotics

Neonatal course:

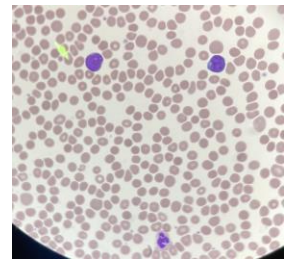
- Baby diagnosed with Transient Leukaemia of Down Syndrome.
- Early complications included hydrops, hepatic dysfunction, renal dysfunction, abnormal coagulation, WCC >100, spontaneous tumour lysis syndrome (urate 0.86), respiratory distress and bilateral pleural effusions.
- Developed congenital pulmonary lymphangectasia, chylothoaracies, severe lymphopaenia with absent B cells in peripheral blood, patent Ductus Arteriosus, right cerebellar haemorrhages and periventricular cystic changes, jaundice of prematurity and conjugated hyperbilirubinaemia.
- Treatments included exchange transfusion, cytarabine, rasburicase, frequent blood product transfusions, IVIG, electrolyte replacement, phototherapy, bilateral intercostal catheters, chest drains and ventilation.
- Though the baby got through the phase of congenital leukaemia, severe ARF and profound cardiorespiratory instability, ongoing complications due to prematurity, Trisomy 21, bilateral PVL and pulmonary lymphangiectasia, with static head growth and inability to be enterally fed, led to the decision to change care pathway to comfort care.
- After 50 days of fighting, the baby passed away peacefully



Ultrasound showing scalp oedema.



Marked skin oedema and pleural effusions



Newborn blood smear – 23% blasts

- Hydrops fetalis is the result of an imbalance in the regulation of fluid leading to an increase in interstitial fluid production or a decrease in lymphatic return.[1]
- In non-immune hydrops fetalis this imbalance can be caused by cardiovascular (21.7%), idiopathic (17.8%), genetic (13.4%), haematological (10.4%), infectious (6.7%), and metabolic (1.1%) issues, as well as chest tumours (6.7%), urogenital issues (2.3%), monochorionic twin complications (5.6%) and gastrointestinal problems (0.5%).[1]
- Though an ultrasound diagnosis, the management and prognosis are dependent on identifying the underlying cause.

- Transient leukaemia of Down Syndrome (TL-DS) is a clonal disorder characterized by circulating megakaryoblasts and dysplastic changes in peripheral blood.[2]
- Between 5-30% of children with Down Syndrome are born with TL-DS, however, despite arising in utero, it is uncommon for TL-DS to present before birth, with <5% of neonatal cases having already been diagnosed antenatally.[2]
- Typical signs of TL-DS in the third trimester are hepatomegaly or splenomegaly (80%), hydrops fetalis (31%), pericardial effusion (23%), aberrant liquor volume (15%), cardiac abnormalities (12.8%), fetal ascites (10%), pleural effusion (8%), and peripheral oedema (3%).[2]
- When fetal blood sampling is performed, blood films show leucocytosis with prominent blasts (96%), thrombocytopenia (86%) and abnormal liver function (92%), the haemoglobin is however usually normal.[2,3]
- Neonatally diagnosed TL-DS has an event-free survival of 63-68%, with early death in 15-23% of cases, and 20-23% of survivors developing acute myeloid leukaemia of Down Syndrome in the first four years of life.[2]
- Antenatally diagnosed TL-DS however, appears to have a much higher fatality rate of 66% based on limited case series data.[2]
- Due to the limited data available, management of antenatal TL-DS is based on anecdotal evidence and neonatal TL-DS protocols.

- Most institutional recommendations for investigating non-immune hydrops fetalis in the late second and third trimester involve genetic testing.
- If no obvious diagnosis is available by ultrasound, consideration should be made to perform fetal blood sampling, to allow not just for genetic testing, but also haematological, infection and EUC/LFT testing, which may allow for early diagnosis of conditions like TL-DS, and subsequently guide decisions on management and expected prognosis, for what can be an acutely unwell fetus.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7356683/. 2) https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15390 3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675407/

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