Introduction

- Hypomethylation at the imprinting control region 2 (IC2) on chromosome 11p15.5 is the commonest identifiable cause of Beckwith-Wiedemann Syndrome (BWS).
- IC2 is located in KCNQ1 intron 10 and is associated with Long QT syndrome (LQTS).
- A recent consensus statement on BWS recommends annual cardiac evaluation including electrocardiogram (ECG) in these patients.
- The natural history of LQTS secondary to hypomethylation at IC2 in BWS is unknown, despite it being the commonest etiology.
- It is also unknown whether adequate attention is paid to the risk of arrhythmias in patients with IC2 lesions by multidisciplinary teams managing patients with this condition.
- Sudden death due to ion channel disease is made on the strength of negative autopsy in addition to ECG, personal / family history or molecular diagnosis of ion channel pathology.
- We report to our knowledge, the first case of infant death attributed to arrhythmia associated with BWS.

Case Report

- A female neonate from in-vitro fertilisation, born to a primigravida mother with benign intracranial hypertension, presented with hypoglycemia on day four of life.
- Congenital hyperinsulinism was confirmed and responded to diazoxide (10mg/kg/day) and chlorothiazide (6.5mg/kg/day).
- BWS was suspected and genetic tests confirmed BWS with hypomethylation at KCNQ1OT1: TSS DMR located within 11p15.5.
- She had gastroschephal reflux disease, which responded to ranitidine. A swallow assessment showed safe swallow.
- Cardiac assessment was normal, including ECG on day 5 of life.
- She tolerated a six hour fast prior to discharge and following this, blood glucose control was excellent.
- Prospective studies are required to examine the natural history of cardiac arrhythmia in BWS patients with IC2 abnormalities.
- Given the location of IC2 in the KCNQ1 gene it is possible that mutations, both genetic and epigenetic, may give rise to both BW and LQT1, the most common variant, is caused by loss of function mutations in KCNQ1 gene.

Discussion

- Hereditary LQTS is an autosomal dominant disorder of cardiac rhythm.
- LQT1, the most common variant, is caused by loss-of-function, heterozygous mutations in KCNQ1, which encodes a protein with structural features of a voltage-gated potassium channel.
- BWS is caused by dysregulation of the expression of imprinted genes in the 11q15.5 region (Figure 1, 2 & 3) which also includes LQT1.
- Hypomethylation at the imprinting control region 2 (IC2) on chromosome 11p15.5 is the commonest identifiable cause of Beckwith-Wiedemann Syndrome (BWS).
- IC2 is located in KCNQ1 intron 10 and is associated with Long QT syndrome (LQTS).
- A recent consensus statement on BWS recommends annual cardiac evaluation including electrocardiogram (ECG) in these patients.
- The natural history of LQTS secondary to hypomethylation at IC2 in BWS is unknown, despite it being the commonest etiology.
- It is also unknown whether adequate attention is paid to the risk of arrhythmias in patients with IC2 lesions by multidisciplinary teams managing patients with this condition.
- Sudden death due to ion channel disease is made on the strength of negative autopsy in addition to ECG, personal / family history or molecular diagnosis of ion channel pathology.
- We report to our knowledge, the first case of infant death attributed to arrhythmia associated with BWS.

Conclusion

- This is to our knowledge, the first report of an infant death attributed to arrhythmia associated with BWS.
- Prospective studies are required to examine the natural history of cardiac arrhythmia in BWS patients with IC2 abnormalities.
- Given the location of IC2 in the KCNQ1 gene it is possible that mutations, both genetic and epigenetic, may give rise to both BWS and LQTS.

References:


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