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A Novel Variant of CACNA1C Subtype Related Disorders: A Neonate with Dysmorphism and Distal Skeletal Defects

Yunis A. Mohamed[1*], Maha Mubarak[1], Jaber Alfaifi[1], Anees Ghassan[1], Hani Hassan[1], Naziha Elreih[1], Osama A. Ibrahim[1]

[1]Department of Pediatrics and Neonatology, Maternity & Children Hospital, 7111, 2307, Bisha 67631, Saudi Arabia

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***Corresponding author:** Yunis A. Mohamed
Department of Pediatrics and Neonatology, Maternity & Children Hospital, 7111, 2307, Bisha 67631, Saudi Arabia

Abstract **Case Report**

The mutation of CACNA1C gene on chromosome 12p13, has known to be associated with disorder with hypotonia, language delay, and skeletal defects with or without seizures (NEDHLSS). We report neonate with a novel variant of CACNA1C subtype related disorder with dysmorphisms and distal skeletal dysplasia.

Keywords: CACNA1C gene, NEDHLSS, CentoXome, whole exome sequencing, neonate with hypotonia and skeletal defect onset.

INTRODUCTION

CACNA1C [MIM 114205] encodes the alpha-1 subunit of a voltage- dependent L-type calcium channel that extended to express in human brain, heart, smooth muscle, and endocrine tissue [1-3]. The common pathogenic variants in CACNA1C include; 1. Timothy syndrome, which manifested by cardiac, limb anomalies, facial dysmorphisms, and neurologic features with autism, seizures, intellectual disability, and hypotonia [4-6]. 2. The, Brugada syndrome, that characterized by ST elevation with symptoms of ventricular arrhythmia, syncope, and sudden death [7-9]. Neurodevelopmental disorder with hypotonia, language delay, and skeletal defects with or without seizures 3. (NEDHLSS) is characterized by global developmental delay apparent from infancy. Affected individuals show severe hypotonia with delayed walking or inability to walk, poor or absent speech, and impaired intellectual development with behavioural abnormalities. Most patients have early-onset seizures, mild skeletal defects that are usually distal, and nonspecific dysmorphic features [10].

The case

A preterm male neonate with dysmorphic features.

Prenatal and Birth History

- Born to 35years old garvida1, para 0 woman
- Spontaneous pregnancy complicated by morbid obesity and bicornate uterus.
- Estimated gestational age: 34weeks +0.
- Prenatal maternal laboratory findings: unremarkable.
- Antenatal scan: revealed possible congenital anomalies.
- Mode of delivery: caesarean delivery secondary to pathological CTG.
- Apgar score: 7and 8 at 1 and 5minutes respectively, not required IPPV.

Progression

Vital signs upon admission

- Heart rate: 140 beats per minute
- Blood pressure: 71/42 mmHg
- Respiratory rate: 53 per minute
- Temperatures: 36.8 C
- Oxygen saturation: 98% on 2liters/minute, nasal cannula oxygen.

Physical examination

- Birth weight: 1730grams, birth length: 42cm, birth head circumference: 31.5cm.
- General appearance: looks dysmorphic, not acute distress, pink, old man face.
- Head: Deformed skull, wide sutures and fontanelles, prominent occipital bone.
- Eyes: Small skin loss of upper eyelid, normal red reflex, no discharge.
- Nose: Depressed nasal bridge, flattened and deviated right nose.
- Neck: short webbing
- Skin: no skin stigmata.

- Skeletal: extended knees, bilateral hyper lax hips, normal upper limbs.
- Mouth: Palate intact, normal tongue, no oral lesions, normal suck, moist mucosa.
- Neurologic: Alert, calm, normal suck, rooting, grasp, and Moro reflexes. Central hypotonia
- Lungs: Clear, equal breath rounds no retractions, no tachypnoea present.
- Cardiovascular: heart sounds are audible, intact femoral pulses. Less than 2 second capillary refill.
- Abdomen: Nontender and non-distended, positive bowel sounds, liver edge just palpable below costal margin.
- Genitourinary: Normal male genitalia, both testicles in scrotum, patent anus.

Laboratory work up

- White blood cell count: 8.66 [10^3/uL], neutrophil; 21.9%, lymphocytes; 64.1%
- Platelets: 195[10^3/uL].
- Hemoglobin: 20.8g/dL.
- Haematocrit: 60%.
- Electrolytes &renal function: within normal range.
- Liver panel: normal
- Euglycemic
- Coagulation profile: normal.
- Blood culture: no growth
- Metabolic screening: normal
- Whole exome sequences (WES): CACNA1C variant c.3108G>Cp.Lys1036Asn detected.

Radiographic work up

- Cranial ultrasound: normal brain anatomy, no bleeding
- Echocardiography: Tiny PDA, PFO.
- Hips ultrasound: normal.

Hospital course

- Total length of stay in NICU: 8 days
- IV ampicillin & gentamicin commenced upon admission and discontinued after 48hours.
- Feeding escalated to full oral adlib at day 4.
- Oxygen weaned at day 2
- Discharge home in a good condition with high risk clinic appointment.

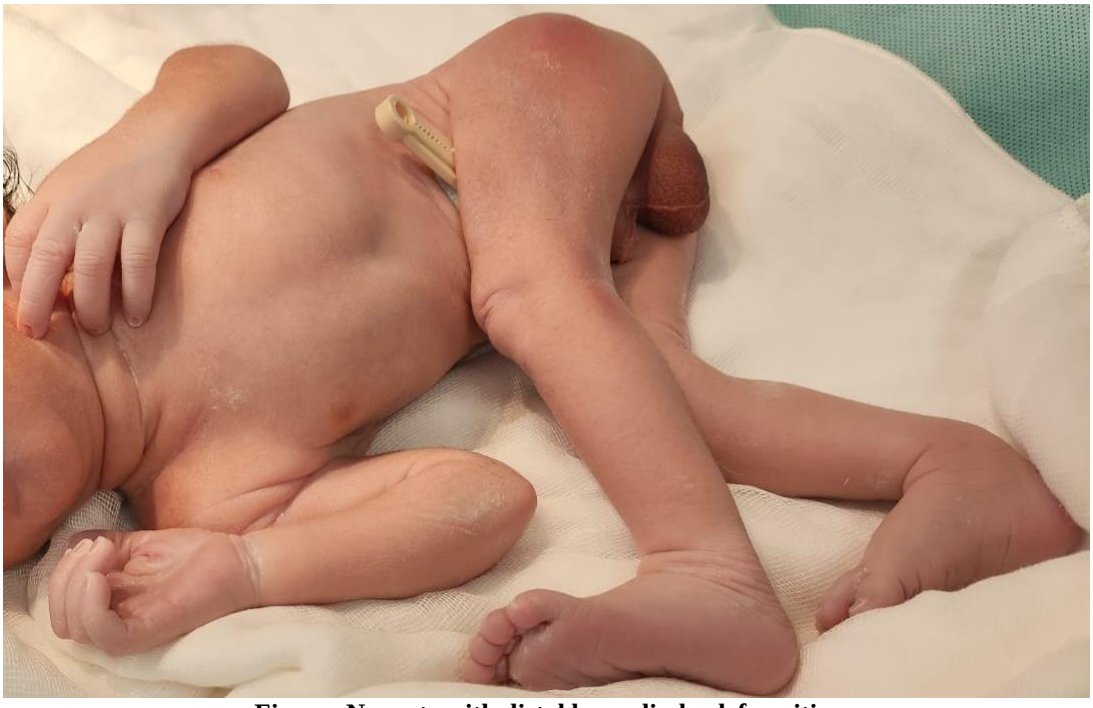

Figure: Neonate with distal lower limbs deformities

DISCUSSION

For the case we reported, the CACNA1C variant c.3108G>p. (Lys1036Asn) causes an amino acid change from lysine to asparagine at position 1036 in exon(s)no.24 of (50). To the best of our knowledge this is a novel variant not previously reported in the literature and it is a first case reported from Bisha maternity and children hospital. It is classified as uncertain significance according to (CENTOGENE and ACMG/AMP ClinGen SVI) recommendations.

Neurodevelopmental disorder with hypotonia, language delay, and skeletal defects with or without seizures (NEDHLSS) is characterized by global developmental delay apparent from infancy. Affected individuals show severe hypotonia with delayed walking or inability to walk, poor or absent speech, and impaired intellectual development with behavioural abnormalities.

Most patients have early-onset seizures, mild skeletal defects that are usually distal, and nonspecific dysmorphic features [10]. CACNA1C encodes the alpha-1 subunit (also known as Cav1.2) of the L-type voltage-dependent calcium channel, which consists of 24 trans-membrane segments that form the pore for ion transport into the cell. It undergoes extensive alternative splicing and has at least 36 different transcripts that are expressed in heart, brain, lung, and smooth muscle [11]. The CACNA1C related NEDHLSS is inherited as autosomal dominant [MIM 114205]. In addition, two individuals with intragenic deletions in CACNA1Cin association with neurodevelopmental and behavioral abnormalities have been previously reported [12]. In the last decades, comparisons of *de novo* 12p13.33 deletions suggested a novel 12p13.33 locus, which includes 9 genes whose deletion is associated to the developmental verbal dyspraxia (DVD), also known as childhood apraxia of speech [13-15]. To our up to date follow up assessment, the patient at his current 6months age, developmentally still has head lag, not sit with support, not yet smile, alert to loud voice, turns from to the other sit from supine position and with normal oral intake.

CONCLUSION

A late preterm 34 weeks baby boy, born via caesarean delivery with dysmorphic features and distal skeletal defects. WES study revealed CACNA1C variant c.3108G>p (Lys1036Asn) which is not reported before in literature.

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