# CASE REPORT

**Hypertonia, Microcephaly and Hyperkalaemia in a Neonate: Coexistence of Neurodevelopmental Disorder and Adrenal Insufficiency**

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## Abstract

In neonates with more than one clinical abnormalities, we always look for a unifying diagnosis that explains the entire clinical presentation. In rare instances, two conditions can co-exist. Here, we report a neonate born out of consanguineous marriage presenting at 48 hours of life with microcephaly, encephalopathy, hypertonia. He had excessive weight loss, persistent hyperkalaemia, shock and elevated level of 17- hydroxyprogesterone. Steroids were started for adrenal insufficiency. Magnetic resonance imaging (MRI) of the brain revealed T2 hyperintensity of cerebral white matter, hypomyelination and parenchymal volume loss causing microcephaly. Clinical exome sequencing (CES) revealed a pathogenic homozygous missense variation of CYP21A2 gene responsible for congenital adrenal hyperplasia and also the presence of a homozygous missense variant of unknown significance (VUS) of VARS gene implicated in neurodevelopmental disorder with microcephaly, seizures, and cortical atrophy (NDMSCA). Baby was neurologically abnormal at discharge. In the setting of consanguinity, there is a possibility of two genetic conditions. Clinical exome sequencing test is useful in demystifying the diagnosis in complex clinical presentation.

**Keywords**: Consanguinity; Microcephaly; Encephalopathy; Hypertonia; Adrenal hyperplasia
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## Introduction

A single unifying diagnosis is always sought in neonates with multiple clinical phenotypes. However, in neonates born out of consanguineous marriage, occurrence of more than one condition in the same child and atypical phenotypes of genetic disorders are known (1). Such complex presentations make diagnosis and phenotypic classification

very difficult. Exome sequencing is preferred when the clinical presentation is atypical and in genetic or clinical heterogeneity (2). Here Here we report a neonate having heterogeneous presentation of hypertonia and hyperkalaemia, which could not be explained by any single condition and was solved by exome sequencing.

## Case report

A term baby boy born at 39 weeks of gestation by vaginal delivery to a multiparous mother out of third degree consanguineous marriage and had normal transition at birth was presented. Elder sibling was 4 years old and developmentally normal for age. Our baby had a birth weight of 2.91 kg, length of 47.5 cm both falling between $10^{th}$ -$50^{th}$ centile for age. Head circumference was 31 cm, which was below $3^{rd}$ centile for age and hence suggestive of microcephaly. These findings had been overlooked and the baby was transferred to postnatal ward for routine care. There were no significant antenatal events and all the antenatal scans were normal. Baby was reported to be well until 48 hours of life and was transferred to the neonatal unit when noted with refusal to feed, irritability, jitteriness, exaggerated startle response and 7% weight loss.

Microcephaly and exaggerated startle response were noted by the admitting team. Baby also had overriding sutures, sloping forehead, hypertelorism and low set ears on examination. In upper limbs, flexor tone was increased. In lower limbs, both flexor and adductor tone were increased as suggested by reduced popliteal, adductor Amiel-Tison angles and difficulty in changing diapers. Neck extensor hypertonia was evident due to the absence of head lag on pull to sit. The presence of dorsal incurvation more than ventral incurvation suggested truncal hypertonia. Deep tendon reflexes including biceps, triceps, knee and ankle reflexes were brisk. Thus, the baby had both axial and appendicular hypertonia. There were no neurocutaneous markers.

Abdominal examination did not reveal any organomegaly or palpable mass. Cardiovascular system and respiratory system were normal. Family history did not reveal similar complaints in any of the members. In addition, the baby also had reduced urine output with progressively rising creatinine and potassium since admission. Prerenal failure secondary to dehydration was considered in view of excessive weight loss. Ultrasound abdomen revealed structurally normal kidneys with normal doppler. However, incidental finding of bilateral enlarged adrenal glands with right adrenal gland having hyperechoic lesion and cystic spaces suggestive of haemorrhage was present.

Differential diagnoses considered for the neurological abnormality were central nervous system malformations, inborn errors of metabolism, hyperekplexia and TORCH (Toxoplasmosis, rubella, cytomegalovirus, herpes, others) infection. Initial investigations for sepsis, cerebrospinal fluid analysis and metabolic screening which included ammonia levels, lactates and urine for ketones turned out to be negative. Electroencephalography was normal. Fundus examination was normal ruling out chorioretinits. Magnetic resonance imaging (MRI) of the brain revealed reduced cerebral parenchymal volume and diffuse hyperintensity involving cerebral white matter in T2 images (Fig. 2). Tandem mass spectrometry (TMS) revealed low carnitine, gas chromatography - mass spectrometry (GCMS) of urine showed increased lactate and plasma amino acid profile showed elevated alanine. Mitochondriopathy was considered as a possibility in view of elevated lactate and alanine.

Urine output gradually improved but potassium continued to increase reaching a peak value of 8.8 mmol/l by day 10 of admission with a corresponding sodium of 122 mmol/litre. (Table 1 & Figure 1) Baby also had poor perfusion requiring a bolus of normal saline. Hyperkalaemia was treated conservatively with insulin dextrose infusion, potassium binding resin which led to resolution of tall T waves on electrocardiogram. 17 hydroxyprogesterone (17 OHP) sent as a part of newborn screening was reported on day 10 of life and was found to be elevated (115 ng/dl). Confirmatory serum 17 OHP was > 200 ng/dl and random cortisol of 5 µg/dl (low). Diagnosis of congenital adrenal hyperplasia (CAH) was made based on the clinical and biochemical findings. Replacement doses of hydrocortisone and fludrocortisone were initiated. Hemodynamic stability was achieved and electrolytes got normalised.

In view of heterogeneous presentation, a sample for clinical exome sequencing (CES) using Nextgen sequencing platform (Illumina platform; 6440 gene panel) was sent. Physiotherapy and early stimulation were initiated during the hospital stay. Parents requested for the discharge of the baby due to logistic reasons by 17 days of life. At the time of discharge, baby was still behind birth weight at 2.7 kg, had a length of 48 cm and head circumference 31 cm. Steroids were continued after discharge. Exome sequencing revealed a pathogenic homozygous missense variation c1069 C>T (p.Arg357Trp) in exon 8 of CYP21A2 gene (mRNA accession number: ENST00000418967.2) responsible for congenital adrenal hyperplasia and also a homozygous missense variant of unknown significance (VUS) c.3212 T>A (p.Leu1071Gln) in exon 27 of VARS gene (mRNA accession number:ENST00000375663.3) which is implicated to cause microcephaly, seizures, cortical atrophy. The in silico predictions of the VARS gene variant was 'probably damaging' by PolyPhen-2 (HumDiv) and 'damaging' by SIFT, LRT and MutationTaster2. Parents were not willing for segregation analysis of the VARS gene. Parents were contacted at 2 months of age and they reported that the baby had failure to thrive, stiffness of limbs and seizures for which the baby was receiving anti-epileptics. He succumbed at 3 months of age.

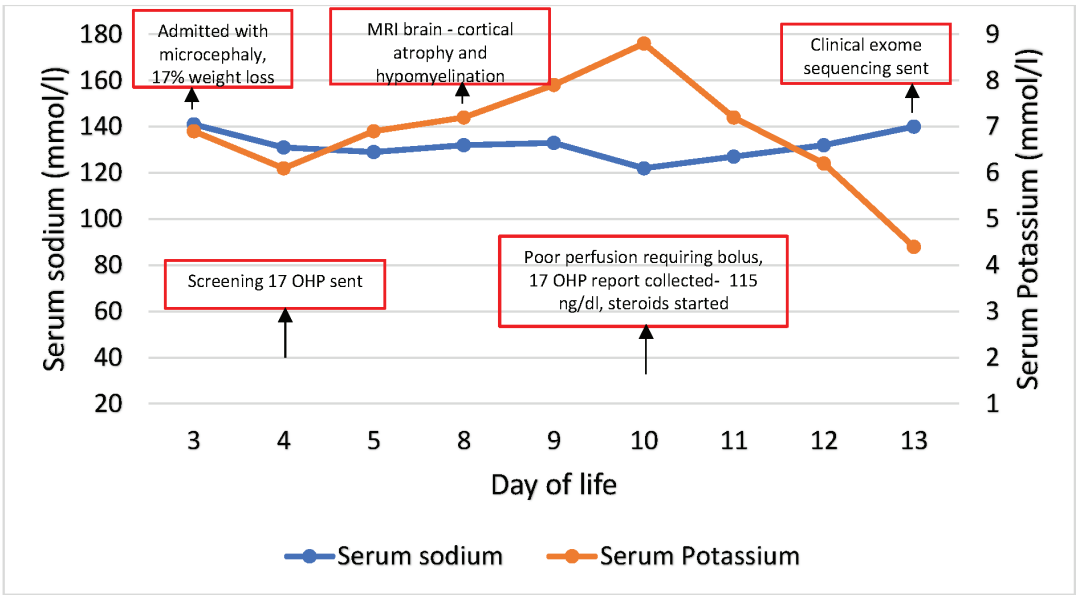


***Figure 1.*** *Trend of electrolytes and sequence of events in our case*

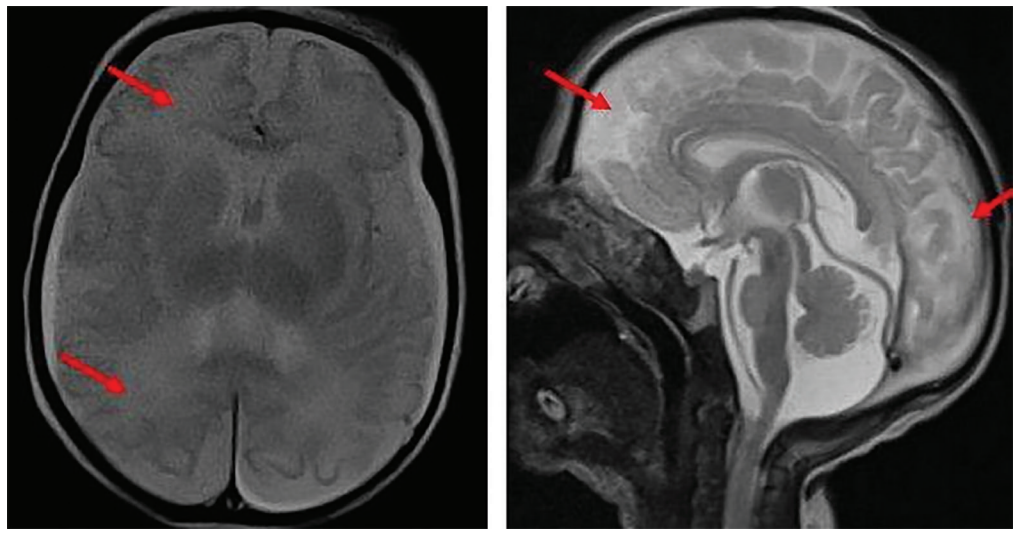

***Figure 2.*** *MRI (T2) image showing reduced cerebral parenchymal volume (microcephaly) and diffuse hyperintensity involving cerebral white matter suggestive of hypomyelination.*

**Table 1.** Serial values of biochemical parameters in our child

| | Day of life | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 9** | **Day 10** | **Day 11** | **Day 12** | **Day 13** |
| Blood urea nitrogen (mg/dl) | 20 | 25 | 46 | 40 | | | | | |
| Serum Creatinine (mg/dl) | 1.0 | 1.0 | 1.6 | 1.6 | | 1.3 | 1.1 | | 0.8 |
| Chloride | | 110 | 108 | 102 | | | | | |
| Serum $Na^+$(mmol/l) | 141 | 131 | 129 | 132 | 133 | **122** | **127** | 132 | 140 |
| Serum $K^+$ (mmol/l) | 6.9 | 6.1 | 6.9 | **7.2** | **7.9** | **8.8** | **7.2** | **6.2** | 4.4 |
| 17-0HP (ng/dl) | | | | | **115 (screening)** | | | **>200 (confirmatory)** | |
| Serum Cortisol (mcg/dl) | | | | | **< 5** | | | | |

## Discussion

Persistent hypertonia from birth is indicative of an in-utero insult or developmental abnormality of the brain (3). Aicardi- Goutieres syndrome and in-utero infections can present with microcephaly and hypertonia. However, MRI did not show any calcification in our case. Schwartz Jampel syndrome, paramyotonia congenita, hereditary hypertonia / Isaac syndrome can present with hypertonia since birth. Likewise, Hyperekplexia can present with dystonia and exaggerated startle response. However, clinical exome sequencing ruled out these syndromes.

We could not explain both hypertonia and adrenal insufficiency (AI) by single etiology. Adrenal hemorrhage has a more common occurrence of 16–29 per 1000 live births as suggested by retrospective studies.(4) However, most newborns with adrenal hemorrhage do not require treatment, as even 10% functional cortisol-producing tissue is sufficient to prevent AI (5) and unilateral hemorrhage like in our case presenting as adrenal

insufficiency is unlikely.(6) Also, it cannot explain the raised 17 OHP levels in our baby. Coincidental adrenal hemorrhage causing AI in a neonate with congenital neurological abnormality was also considered.

Frequency of autosomal recessive disorders is high in the regions with high rate of consanguinity and co-occurrence of 2 or more diseases in the same individual has also been rarely reported. Ali et al., (7) Stephen et al., (8) Fadda et al., (9) have previously reported complex phenotypes with occurrence of more than 1 disease in the same child similar to our case and all three were born out of either second or third degree consanguineous marriage.

Mutation in CYP21A2 gene due to amino acid substitution of Tryptophan for Arginine at codon 357 is previously reported to cause 21 hydroxylase deficiency (10). A potentially novel missense mutation in the VARS gene, not previously known, was reported as VUS in our case. A total of 10 patients with VARS gene mutation have been reported till now (11,12). VARS gene encodes the only known valine cytoplasmic-localized aminoacyl-tRNA synthetase which is required for protein translation and gene deficiency is associated with neurodevelopmental disorder with microcephaly, seizures, and cortical atrophy (NDMSCA). In the case series of 7 patients with bi-allelic missense mutation in the VARS gene (11), microcephaly at birth was present in one of them while the others developed microcephaly during infancy. Among them, one had global hypertonia similar to our child. Earliest age of onset of seizures was on day 2.

Spectrum of MRI findings in VARS gene deficiency ranges from T2 hyperintensities, hypomyelination, cerebral volume loss to cortical atrophy.(11) Our baby had a typical clinical phenotype associated with the gene deficiency in the form of microcephaly, global hypertonia since birth and reduced cerebral parenchymal volume, white matter hyperintensity in MRI. Further MRI at a later age might have revealed progressive cortical atrophy.

VUS if associated with typical clinical phenotype and heterozygous mutation on segregation analysis of the parents can be reclassified as likely pathogenic. This can guide during the next pregnancy for antenatal diagnosis and management. Our neonate had typical phenotype but sangers sequencing could not be done in the parents.

As two thirds of the population can potentially carry more than one gene variant, it is not surprising that our neonate had two genetic conditions, though as clinicians we search for unifying diagnosis. The possibility of having 2 genetic conditions should be considered more so in a consanguineous union. VARS gene mutation though very rare, should be considered in neonates with global hypertonia and microcephaly. Clinical exome sequencing is useful in demystifying the diagnosis in complex clinical presentation when other investigations are inconclusive.

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None

## Author's Contribution

Usha Devi, Nirmalan, Prakash, Umamaheswari managed the patient.

Usha Devi and Umamaheswari reviewed the literature and drafted the initial version of the manuscript. Prakash, Nirmalan contributed to literature review and critically revised the manuscript. All the authors contributed to drafting

of the manuscript and approved the final version of the manuscript.

## Conflict of interest

None

## References


1. Shawky RM, Elsayed SM, Zaki ME, Nour El-Din SM, Kamal FM. Consanguinity and its relevance to clinical genetics. Egyptian Journal of Medical Human Genetics 2013;14:157–64.
2. Ankala A, Hegde MR. Gamut of genetic testing for neonatal care. Clin Perinatol 2015;42:217–26, vii.
3. Hart AR, Sharma R, Rittey CD, Mordekar SR. Neonatal hypertonia - a diagnostic challenge. Dev Med Child Neurol 2015;57:600–10.
4. Gyurkovits Z, Maróti Á, Rénes L, Németh G, Pál A, Orvos H. Adrenal haemorrhage in term neonates: a retrospective study from the period 2001–2013. The Journal of Maternal-Fetal & Neonatal Medicine 2015;28:2062–5.
5. Simon DR, Palese MA. Clinical update on the management of adrenal hemorrhage. Curr Urol Rep 2009;10:78–83.
6. Zessis NR, Nicholas JL, Stone SI. Severe bilateral adrenal hemorrhages in a newborn complicated by persistent adrenal insufficiency. Endocrinol Diabetes Metab Case Rep (Internet) 2018 (cited 2020 Apr 17);2018. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5820741/
7. Ben Haj Ali A, Amouri A, Sayeb M, Makni S, Hammami W, Naouali C, et al. Cytogenetic and molecular diagnosis of Fanconi anemia revealed two hidden phenotypes: Disorder of sex development and cerebro-oculo-facio-skeletal syndrome. Mol Genet Genomic Med (Internet) 2019 (cited 2020 May 9);7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6625148/
8. Stephen J, Nampoothiri S, Vinayan KP, Yesodharan D, Remesh P, Gahl WA, et al. Cortical atrophy and hypofibrinogenemia due to FGG and TBCD mutations in a single family: a case report. BMC Med. Genet. 2018;19:80.
9. Fadda A, Butt F, Tomei S, Deola S, Lo B, Robay A, et al. Two hits in one: whole genome sequencing unveils LIG4 syndrome and urofacial syndrome in a case report of a child with complex phenotype. BMC Med Genet (Internet) 2016 (cited 2020 May 9);17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5114772/
10. Chiou SH, Hu MC, Chung BC. A missense mutation at Ile172----Asn or Arg356----Trp causes steroid 21-hydroxylase deficiency. J. Biol. Chem. 1990;265:3549–52.
11. Friedman J, Smith DE, Issa MY, Stanley V, Wang R, Mendes MI, et al. Biallelic mutations in valyl-tRNA synthetase gene VARS are associated with a progressive neurodevelopmental epileptic encephalopathy. Nat Commun 2019;10:1–10.
12. Karaca E, Harel T, Pehlivan D, Jhangiani SN, Gambin T, Akdemir ZC, et al. Genes that affect brain structure and function identified by rare variant analyses of Mendelian neurologic disease. Neuron 2015;88:499–513.