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Case Report

Paediatrics Section

Rubinstein-Taybi Syndrome in a Toddler with Refractory Seizures and Congenital Heart Disease: A Case Report

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ABSTRACT

Rubinstein-Taybi Syndrome (RTS) is a rare congenital genetic disorder characterised by distinctive facial dysmorphism, broad thumbs and halluces, postnatal growth retardation, intellectual disability, and variable multisystem involvement. It is most commonly caused by pathogenic variants in the CREB-Binding Protein (CREBBP) gene and less frequently by mutations in the EP300 (E1A-binding protein p300) gene. Owing to marked phenotypic variability and overlap with other syndromic conditions, diagnosis is often delayed, particularly in early childhood. Neurological manifestations such as seizures, although relatively uncommon, are clinically significant and may be severe. The present case report describes an 18-month-old male child who presented with fever, respiratory symptoms, and refractory generalised tonic-clonic seizures. The patient had a history of recurrent pneumonia and had previously undergone surgical correction for Congenital Heart Disease (CHD), including ventricular septal defect and patent ductus arteriosus. Developmental evaluation revealed global developmental delay with growth retardation. Physical examination showed microcephaly, characteristic facial dysmorphism, broad thumbs and halluces, and bilateral cryptorchidism. Neuroimaging demonstrated ventriculomegaly with a periventricular granulomatous lesion. Cerebrospinal fluid culture grew Candida species. Whole-exome sequencing later identified a pathogenic CREBBP gene variant, confirming RTS type 1. The present case highlights the importance of recognising the characteristic clinical constellation of RTS in children presenting with seizures and CHD. Early diagnosis facilitates appropriate multidisciplinary management, anticipatory guidance, and genetic counselling. Reporting the current case adds to the limited literature on severe neurological presentations of RTS and underscores the need for heightened clinical awareness.

Keywords: Global developmental delay, Recurrent infections, Whole-exome sequencing

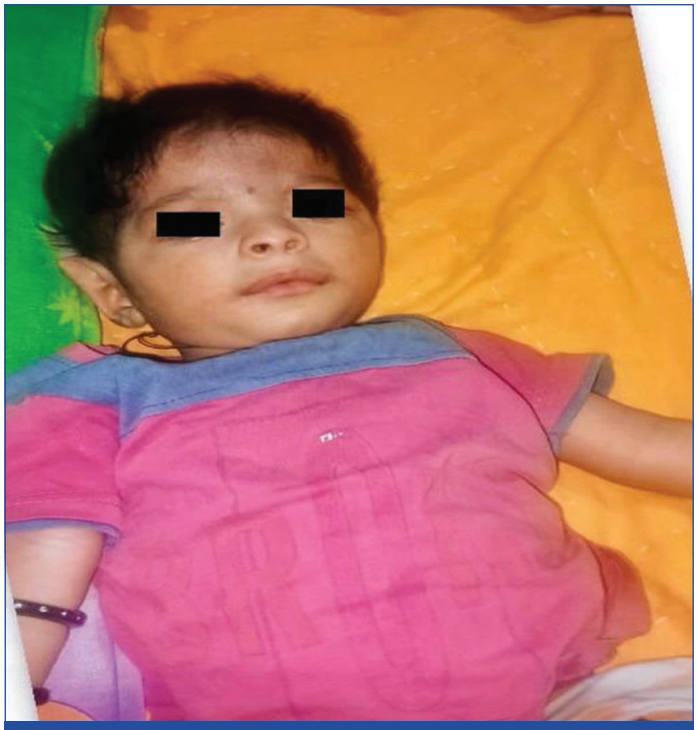
CASE REPORT

An 18-month-old male child presented with fever, cough, and cold for 6-7 days, followed by multiple episodes of refractory generalised tonic-clonic seizures on the day of admission. The seizures episodes were independent of fever spikes and showed poor response to first-line antiepileptic therapy. There was no history of trauma, toxin exposure, or previous seizure episodes. The child was a known case of CHD and had undergone surgical correction for ventricular septal defect with patent ductus arteriosus at one year of age. There was a history of recurrent pneumonia requiring hospitalisation on two occasions during the previous six months. The child was apparently well until 6-7 days prior to admission, when he developed low-grade fever associated with cough and coryza. The fever was intermittent, moderate in intensity, not associated with chills or rigours, and partially relieved with antipyretics. There was no history of rash, vomiting, loose stools, or decreased urine output. Respiratory symptoms were not associated with fast breathing, chest retractions, or cyanosis.

On the day of admission, the child developed sudden-onset generalised tonic-clonic seizures characterised by loss of consciousness, up-rolling of the eyes, tonic stiffening followed by clonic jerking of all four limbs, drooling of saliva, and post-ictal drowsiness. Recurrent seizure episodes each lasted approximately 2-3 minutes, with incomplete recovery of baseline sensorium between episodes. There was no history of focal onset, asymmetry of movements, or automatisms. Despite administration of intravenous levetiracetam and sodium valproate at the referring centre, the child continued to have recurrent seizures without regaining consciousness in between episodes, fulfilling criteria for refractory status epilepticus. There was no history suggestive of central nervous system infection, such as persistent vomiting, altered cry, bulging fontanelle, or photophobia. No regression of previously attained developmental milestones was noted during the current illness. The child was born at term by normal vaginal delivery to non-consanguineous parents, with a birth weight of 2.5 kg. There was no history of perinatal asphyxia or neonatal intensive care unit admission. Immunisations were up to date for age. Both parents and an elder sibling (three-year-old female child) were clinically healthy, with no family history of congenital anomalies, seizures, or developmental delay.

Developmental assessment revealed global developmental delay (developmental quotient ~49%) [1]. Gross motor milestones were delayed, with the child able to sit only with support. Fine motor development was relatively preserved with the presence of a pincer grasp. Language development was limited to cooing sounds, while socially the child recognised his mother. On physical examination, weight (5.5 kg), length (62 cm), and head circumference (40 cm) were below the third centile for age [2]. Facial dysmorphism included down-slanting palpebral fissures, low anterior hairline, convex nasal bridge, smooth philtrum, and hirsutism over the forehead [Table/Fig-1]. Broad thumbs and halluces were noted, along with bilateral cryptorchidism. A median sternotomy scar was present over the chest. Cardiovascular examination revealed normal heart sounds with no audible murmurs.

Neurological examination showed the child to be sedated with ongoing continuous convulsive activity. Pupils were bilaterally equal and sluggishly reactive to light. Motor examination revealed generalised hypertonia with preserved deep tendon reflexes and bilateral flexor plantar responses. Higher mental functions, sensory examination, cerebellar signs, and detailed cranial nerve examination could not be assessed due to sedation. Respiratory and abdominal examinations were within normal limits. Blood



[Table/Fig-1]: Clinical photograph of child showing dysmorphic facial features.

pressure was (77/42 mmHg) persistently below the 50th centile for age [1].

A provisional diagnosis of refractory status epilepticus in an operated case of ventricular septal defect with patent ductus arteriosus, with bilateral bronchopneumonia, global developmental delay, and syndromic features was considered.

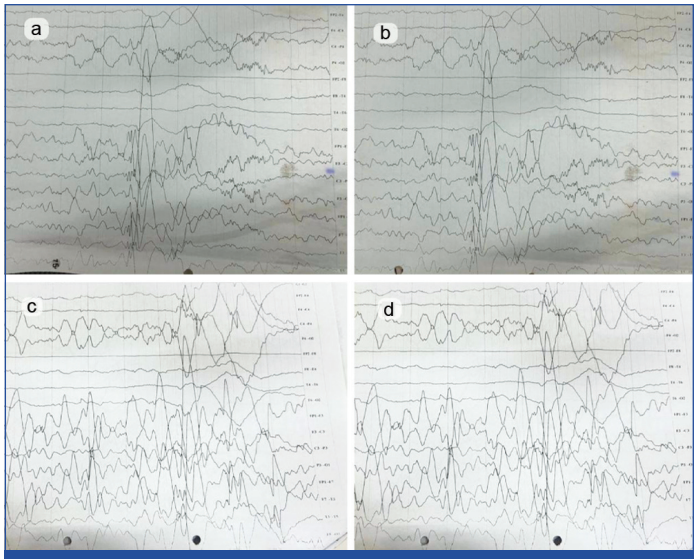
Management

Day 1 (Admission): The child was admitted to the Paediatric Intensive Care Unit and remained hospitalised for 30 days. Routine laboratory investigations revealed leukocytosis and elevated C-reactive protein. Empirical intravenous antibiotics were initiated after sending blood cultures, which showed no growth. Fundus examination revealed no evidence of papilloedema. Refractory status epilepticus persisted despite full therapeutic doses of intravenous levetiracetam (60 mg/kg/dose), sodium valproate (30 mg/kg/day), and phenobarbital (5 mg/kg/day). Continuous midazolam infusion was escalated to 6 µg /kg/min, and the child required mechanical ventilation.

Day 2-3: The child developed refractory shock requiring haemodynamic support with dobutamine, adrenaline, noradrenaline, and vasopressin. Two-dimensional echocardiography demonstrated postoperative Ventricular Septal Defect (VSD) closure with Patent Ductus Arteriosus (PDA) ligation, dilated left-sided chambers, and severely reduced left ventricular ejection fraction (20-25%), suggestive of myocardial dysfunction. Considering possible viral myocarditis with encephalitic involvement, intravenous immunoglobulin was administered, following which transient neurological improvement occurred and repeat echocardiography showed improvement in ejection fraction to 40-45%. Karyotyping was sent due to dysmorphic features, multisystem involvement, and severe neurological manifestations.

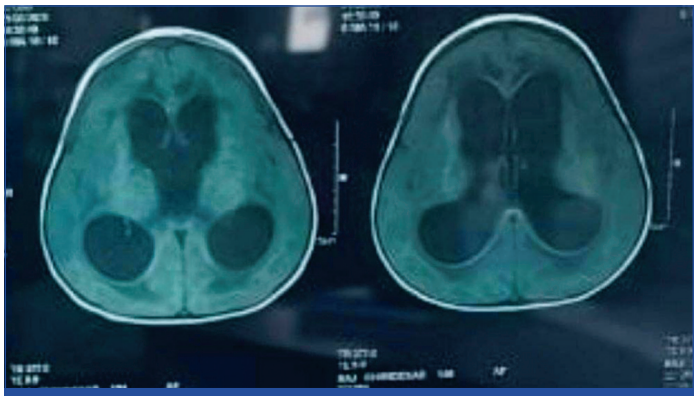
Day 7-14: Seizures persisted intermittently. Progressive increase in head circumference (~2 cm over two weeks) raised concern for raised intracranial pressure. Electroencephalography (EEG) showed epileptiform abnormality predominantly from left hemisphere spike-wave discharges followed by electrodecrement [Table/Fig-2a-d].

The Magnetic Resonance Imaging (MRI) brain revealed ventriculomegaly involving the lateral, third, and fourth ventricles, with a well-defined approximately 1.0×0.9×0.8 cm altered signal

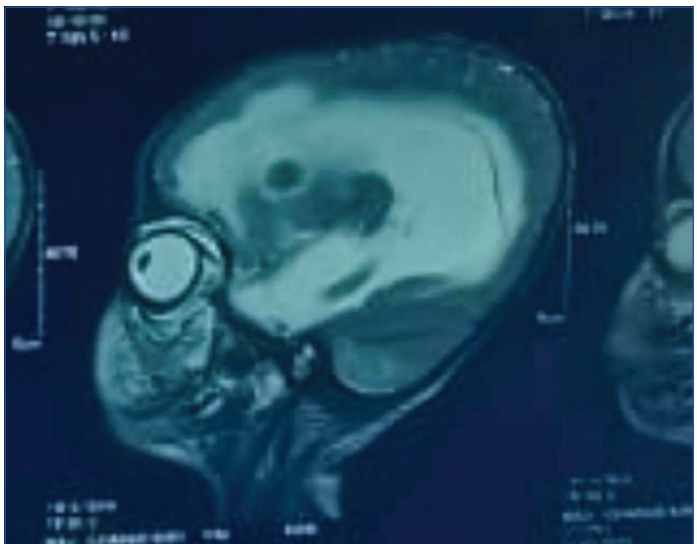


[Table/Fig-2]: a) Top left tracing; b) Top right tracing; c) Bottom left tracing; d) Bottom right tracing: Abnormal EEG suggestive of epileptiform abnormality predominantly from left hemisphere.

lesion in the right frontal periventricular region, suggestive of a granulomatous lesion [Table/Fig-3,4].



[Table/Fig-3]: Axial MRI image demonstrating moderate to gross dilatation of ventricles.

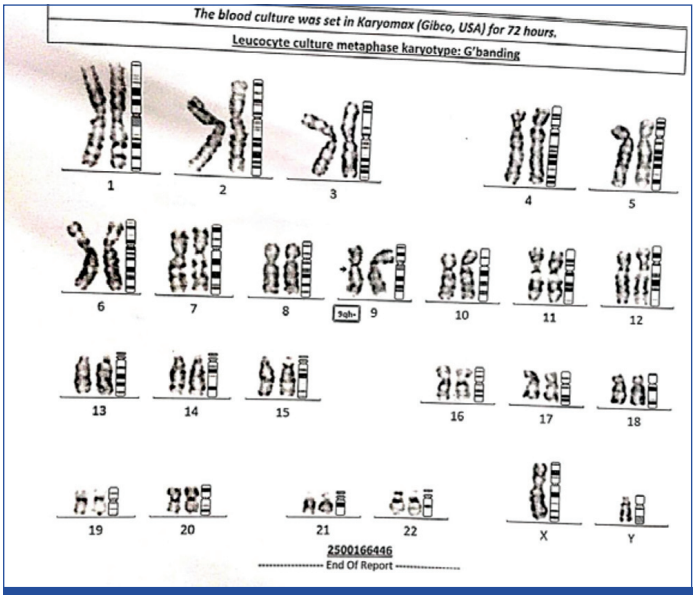


[Table/Fig-4]: Sagittal T2 weighted MRI image showing gross ventriculomegaly with periventricular lesion.

Tuberculosis was considered due to endemic prevalence and radiological findings. Gastric aspirate Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) was non-reactive. Empirical antitubercular therapy was initiated but no clinical improvement occurred. Fungal Central Nervous System (CNS) infection was also considered. Intravenous fluconazole was initiated, and cerebrospinal fluid culture subsequently grew Candida species, confirming fungal CNS infection. Due to progressive ventriculomegaly, an external

ventricular drain was placed for cerebrospinal fluid diversion, without significant clinical improvement.

Day 15-30: Karyotyping was sent which turned to be normal (46,XY). Whole-exome sequencing was sent considering genetic abnormality [Table/Fig-5]. Despite aggressive multidisciplinary management, the child continued to have refractory seizures and persistent cardiovascular instability. The clinical condition progressively deteriorated, and the child developed sudden cardiorespiratory arrest. Resuscitative measures were unsuccessful, and the child succumbed to illness. Posthumously, whole-exome sequencing revealed a heterozygous pathogenic CREBBP exon 28 deletion, consistent with autosomal dominant RTS type 1. An additional heterozygous likely pathogenic variant in the Bestrophin 1 (BEST 1) gene was also identified [Table/Fig-6,7].



[Table/Fig-5]: Karyotyping of patient suggestive of normal male chromosomes.

Gene	Chromosomes Locus	Protein
CREBBP	16p13.3	CREB-binding protein (Cyclic AMP Response Element-Binding protein)
EP300	22q13	Histone acetyltransferase p300

[Table/Fig-8]: Gene implicated in Rubinstein-Taybi Syndrome (RTS) showing chromosomal locus and encoded protein.
AMP: Adenosine monophosphate

regulation of gene expression during neurodevelopment. Disruption of CREBBP-mediated transcriptional regulation may impair neuronal differentiation, synaptic maturation, and cortical network development, thereby predisposing affected individuals to epileptogenesis and neurodevelopmental impairment [5,8]. Clinical studies indicate that seizures in RTS demonstrate heterogeneous presentations and may occasionally be difficult to control, particularly in patients with associated structural brain abnormalities or superimposed neurological insults [5,6]. In the present case, the child developed early-onset epilepsy that rapidly progressed to refractory and super-refractory status epilepticus, reflecting a severe neurological phenotype likely influenced by underlying genetic susceptibility together with ventriculomegaly and concurrent central nervous system infection.

The CHD is reported in approximately one-third of RTS patients, with ventricular septal defect being the most common anomaly [9,10]. Stevens CA et al., and Bentivegna A et al., demonstrated that cardiac involvement significantly worsens prognosis, particularly when combined with neurological disease [9,10]. Literature describes chronic hypoxemia, impaired cerebral perfusion, and haemodynamic instability as contributors to adverse neurological outcomes. In the present patient, CHD significantly restricted aggressive neurocritical care strategies, including fluid resuscitation, sedative escalation, and osmotherapy, thereby amplifying neurological vulnerability [9,10]. Similar syndromic cases in the literature describe this bidirectional vulnerability, where cardiac disease worsens neurological injury and neurological instability precipitates cardiovascular decompensation,

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
CREBBP(-) (ENST00000262367.10)	Exon 28	c.4650_4654 del p.Glu1551 HisfsTer2	Heterozygous	Rubinstein-Taybi syndrome 1 (OMIM#180849)	Autosomal dominant	Pathogenic (PVS1,PM2,PP5)

[Table/Fig-6]: Genetic analysis identifying a heterozygous pathogenic CREBBP deletion variant.
OMIM: Online mendelian inheritance in man

Gene, Variant details	Zygosity Depth (Alt allele %)	In silico tools	MAF	Literature	OMIM Disease	Inheritance	Classification
BEST1 (+) c.725_726del p.Val242GlyfsTer26 ENST00000378043.9	Heterozygous 63X(58.7%)	MT2-D	1000 G-NA gnomAD (V2.1) -NA gnomAD (V3.1) -NA MedVar-0.001%	CLINVAR ID - 1075048	Macular dystrophy, vitelliform, 2 (OMIM#153700) Retinitis pigmentosa-50 (OMIM#613194) Vitreoretinochoroidopathy (OMIM#193220)	Autosomal dominant	Likely Pathogenic

[Table/Fig-7]: Summary of a heterozygous likely pathogenic variant in the BEST1 gene, associated with retinal disorders including vitelliform macular dystrophy, retinitis pigmentosa-50, and vitreoretinochoroidopathy, inherited in an autosomal dominant manner.
Abbreviation: D: Damaging; Prd: Probably damaging; BN: Benign; T: Tolerated; MAF: Minor allele frequency; MedVar: MedGenome Internal database; MT2: MutationTaster2; Alt allele - Alternate allele

DISCUSSION

The RTS is a rare multisystem genetic disorder caused primarily by pathogenic variants in the CREBBP gene (RTS type 1) and less commonly in EP300 (RTS type 2) [3-5]. It is characterised by distinctive facial dysmorphism, broad thumbs and halluces, growth retardation, intellectual disability, and multisystem involvement [Table/Fig-8] [3,4].

Neurological manifestations of RTS commonly include global developmental delay, epilepsy, ventriculomegaly, and various structural brain abnormalities [6,7]. These features are largely attributed to pathogenic variants in the CREBBP gene, which encodes a transcriptional co-activator with histone acetyltransferase activity that plays a critical role in chromatin remodelling and creating a vicious cycle that complicates intensive care management and worsens survival outcomes [7,8]. RTS frequently presents as a complex multisystem disorder, and diagnosis is often delayed when early phenotypic features are subtle or overshadowed by acute medical conditions [2,3]. Overlapping manifestations such as developmental delay, seizures, feeding difficulties, recurrent infections, and growth failure often lead to fragmented symptom-based management rather than early syndromic recognition. This diagnostic delay is well documented in the literature and contributes to delayed genetic confirmation and delayed implementation of anticipatory surveillance strategies [2].

Management is further complicated by altered drug pharmacokinetics, intellectual disability, feeding difficulties,

multisystem involvement, and frequent comorbid infections. In critically ill children, systemic inflammation, metabolic derangements, electrolyte imbalance, raised intracranial pressure, and CNS infections markedly lower seizure threshold, frequently precipitating refractory or super-refractory status epilepticus. These factors create a treatment-resistant epileptic phenotype, necessitating intensive care management and often resulting in poor neurological outcomes [5,6].

Management of complex RTS cases requires coordinated multidisciplinary care involving neurology, cardiology, genetics, intensive care, infectious disease, and rehabilitation services. Therapeutic decision-making is complicated by fragile physiological reserves, competing system priorities, and high susceptibility to infection. In patients with severe neurological disease, CHD, and CNS infection, treatment strategies often shift from curative intent to stabilisation and supportive care [2].

The neurological deterioration in this child was multifactorial. Structural abnormalities, ventriculomegaly, and a periventricular granulomatous lesion formed a vulnerable epileptogenic substrate. Superimposed Candida meningitis further impaired CSF dynamics, increased intracranial pressure, and worsened seizure control. Fungal CNS infections in critically ill children are associated with high mortality and poor neurological outcomes [11]. Whole-exome sequencing remains the gold standard for diagnosis in syndromic children with refractory neurological disease and multisystem involvement [4,5]. In the present case, genetic confirmation explained the complex phenotype, although delayed diagnosis and overlapping infections limited therapeutic benefit.

Whole-exome sequencing also identified a heterozygous likely pathogenic variant in the BEST1 gene. Pathogenic variants in BEST1 are associated with a group of retinal disorders collectively termed bestrophinopathies, including Best vitelliform macular dystrophy, autosomal dominant vitreoretinochoroidopathy, and retinitis pigmentosa-50. The BEST1 gene encodes bestrophin-1, a calcium-activated anion channel predominantly expressed in the retinal pigment epithelium and plays an important role in retinal ion transport and photoreceptor function [12]. Although the child did not demonstrate overt retinal abnormalities during life, this finding may represent an incidental genetic variant. Nevertheless, its identification has implications for genetic counselling because BEST1-related retinopathies are commonly inherited in an autosomal dominant pattern and may warrant ophthalmological evaluation and family screening in at-risk relatives.

CONCLUSION(S)

The RTS should be considered in children presenting with characteristic facial dysmorphism, broad thumbs and halluces, developmental delay, seizures, and CHD. The current case highlights the severe neurological phenotype of RTS, including refractory status epilepticus and ventriculomegaly, leading to a fatal outcome due to overlapping genetic vulnerability and infectious complications. Early syndromic recognition, timely molecular genetic confirmation using whole-exome sequencing, and multidisciplinary management are essential for accurate diagnosis, prognostication, genetic counselling, and care planning. However, severe phenotypes may still carry a poor prognosis despite optimal therapy and advanced intensive care support.

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