Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Rasmussen's encephalitis in Turner's syndrome needing a functional hemispherotomy - Coincidence or Connection?

Sumit Malgaonkar
Sree Chitra Thirunal Institute for Medical Sciences and Technology
Pooja Choudhary
Sree Chitra Thirunal Institute for Medical Sciences and Technology
George Chandy Vilanilam
gvil99@yahoo.com
Sree Chitra Thirunal Institute for Medical Sciences and Technology
Ramshekhar Menon
Sree Chitra Thirunal Institute for Medical Sciences and Technology
Ashalatha Radhakrishnan
Sree Chitra Thirunal Institute for Medical Sciences and Technology
Krishnakumar K
Sree Chitra Thirunal Institute for Medical Sciences and Technology

Case Report

Keywords: Rasmussen's encephalitis, Turner syndrome, Hemispherotomy, Autoimmunity, Pediatric epilepsy

Posted Date: June 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9461352/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Rasmussen’s encephalitis (RE) is a progressive immune-mediated epileptic encephalopathy characterized by drug-resistant focal seizures and hemispheric epilepsy. Turner’s syndrome (TS), due to monosomy X and several systemic anomalies, is associated with increased autoimmune susceptibility. Their coexistence has not been previously reported and raises the question of a chance association versus a pathophysiological connection.

An eight-year-old girl with karyotype-proven TS presented with a two-year history of progressive focal seizures refractory to multiple anti-seizure medications. MRI demonstrated progressive right hemispheric atrophy involving the frontal lobe, insula, and hippocampus. Video-EEG confirmed right frontocentral ictal onset. Despite immunotherapy, seizures persisted, and she underwent right functional hemispherotomy with early postoperative seizure freedom.

This case highlights a novel association between TS and RE, suggesting a potential immunogenetic link mediated by X-linked immune dysregulation.

Introduction

Rasmussen’s encephalitis (RE) is a rare, chronic inflammatory disorder of childhood presenting with drug-resistant focal seizures, progressive neurological decline, and unilateral hemispheric atrophy [1–3]. It is now recognized as a cytotoxic T-cell–mediated autoimmune encephalitis directed against neuronal antigens [2, 4]. Although immunotherapies such as corticosteroids, intravenous immunoglobulin, and rituximab may transiently reduce seizure burden, hemispherotomy remains the definitive treatment for durable seizure control [5–7].

Turner’s syndrome (TS), caused by complete or partial monosomy of the X chromosome, affects approximately 1 in 2,500 female births and is associated with a significantly increased prevalence of autoimmune disorders, including autoimmune thyroiditis and type 1 diabetes mellitus [8–10]. This predisposition is attributed to haploinsufficiency of X-linked immune regulatory genes, altered cytokine profiles, and impaired immune tolerance [11–14].

Despite overlapping immunological mechanisms, the coexistence of RE and TS has not been previously reported and draws a though to a possible immunogenetic pathophysiological connection. We describe the first such case and discuss its potential immunogenetic and prognostic implications.

Case report

An eight-year-old girl, the first child of non-consanguineous parents, presented with a two-year history of progressive focal seizures. The initial events began at six years of age as brief episodes of left facial twitching associated with impaired awareness lasting 10–15 seconds. Over the following months, seizure semiology evolved to include auditory auras described as 'hearing songs', visual hallucinations,

forced deviation of the eyes to the left, and perioral automatisms. The seizures increased in frequency, occurring in clusters on multiple days each month despite escalating anti-seizure therapy.

She received polytherapy with levetiracetam, valproate, clobazam, phenytoin, phenobarbital, and lacosamide without sustained seizure control and no notable drug adverse events.

On examination, she was short statured for age (< 3rd centile) with subtle dysmorphic features consistent with Turner syndrome. Neurological examination revealed left upper motor neuron facial weakness without significant limb motor deficit. Cognitive function was preserved. Karyotyping confirmed monosomy X (45,X).

Video-EEG monitoring demonstrated a well-formed posterior dominant rhythm with superimposed right frontocentral slowing. Frequent interictal epileptiform discharges were noted over the right frontal and frontocentral regions. Multiple habitual seizures were captured, each characterized by low-voltage fast activity over the right frontocentral leads evolving into rhythmic discharges spreading within the right hemisphere. No independent contralateral ictal onset was observed.

MRI brain revealed progressive right hemispheric cortical atrophy with T2/FLAIR hyperintensity involving the superior and middle frontal gyri, insular cortex, and hippocampus on serial imaging, fulfilling diagnostic criteria for Rasmussen's encephalitis [6, 15].Arterial spin labelling(ASL) showed right hemispheric hypoperfusion.Cardiac and other systemic evaluation was within normal limits.

Cerebrospinal fluid analysis showed mild lymphocytic pleocytosis, with negative autoimmune antibody panel.

The patient initially underwent immunotherapy including repeated cycles of intravenous immunoglobulin, pulsed corticosteroids, and rituximab, resulting in only transient reduction in seizure frequency. Given persistent disabling seizures and radiological progression, she was evaluated by a multidisciplinary epilepsy surgery team for surgical candidacy assessment.Due to good clinico-radiological concordance,she was planned for a right functional hemispherotomy.

She subsequently underwent right functional hemispherotomy using a modified Delalande(vertical) technique, including frontobasal,insular,temporal and parieto occipital disconnection, transventricular complete callosotomy, and mesial temporal resection. Postoperatively, she achieved seizure freedom(Engel class I at 8 months follow up) with mild left hemiparesis which improved subsequently.

Discussion

This report documents the first known coexistence of Rasmussen's encephalitis and Turner syndrome, suggesting a potential shared mechanism of immune dysregulation.

RE is characterized by antigen-specific $CD8^+$ cytotoxic T-cell–mediated neuronal injury, resulting in progressive hemispheric dysfunction [2,4]. In contrast, TS is associated with systemic immune

imbalance, including reduced regulatory T-cell function, skewed X-chromosome inactivation, and increased susceptibility to autoimmune disorders [10–12].

X-linked immune regulatory genes such as FOXP3, TLR7, and CD40L play key roles in immune tolerance and inflammatory signalling [13,16,17]. Haploinsufficiency or dysregulated expression of these genes in TS may result in impaired immune regulation, thereby predisposing to aberrant cytotoxic immune responses and localized cortical inflammation as observed in RE.

RE has previously been associated with other autoimmune or dysgenetic conditions, including type 1 diabetes mellitus, Hashimoto thyroiditis, and linear scleroderma [18–21], supporting the concept of a broader autoimmune spectrum (Table 1A,1B). The present case extends this spectrum to include Turner syndrome.

From a clinical standpoint, early recognition by seizure semiology,MRI and video EEG are essential. While immunotherapy may delay disease progression, hemispherotomy remains the most effective intervention for long-term seizure control, achieving seizure freedom in a majority of pediatric patients [7,22]. Ruling out systemic anomalies of Turner's like coarctation of aorta and hypertension prior to surgery are essential.The favorable outcome in our patient supports early surgical consideration in appropriately selected cases and confirms good post surgical outcomes as in other cases of Rasmussen's.

Table 1A. Autoimmune and systemic associations reported with Rasmussen's encephalitis

Condition	Clinical relevance
Type 1 diabetes mellitus	Shared T-cell–mediated autoimmunity
Hashimoto thyroiditis	Thyroid autoimmunity overlap
Linear scleroderma	Cutaneous–CNS autoimmune association
Anti-GAD65 epilepsy	Overlapping antibody-mediated epilepsy
Turner syndrome (present case)	X-linked immune dysregulation (novel association)

Table 1 B. X-linked immune genes relevant to autoimmunity and potential relevance to Rasmussen's encephalitis

Gene	Function	Mechanism in TS	Possible relevance to RE
FOXP3(Xp11.23)	Regulatory T-cell differentiation	Haploinsufficiency → impaired tolerance	Loss of control of autoreactive $CD8^+$ T cells
KDM6A/UTX(Xp11.3)	Epigenetic regulation of immune enhancers	Reduced expression → altered T-cell transcription	Broad immune dysregulation
TLR7 (Xp22.2)	Innate RNA sensor, IFN-I pathway	Escapes XCI; dosage imbalance	Hyperactive autoimmune response
CXorf21/TASL(Xp22.2)	Adaptor for TLR7–SLC15A4 signalling	Dosage-sensitive activation	Amplified interferon cascade
IRAK1 (Xq28)	Kinase in TLR/IL-1R pathway	Dosage-dependent inflammatory bias	Enhanced Th1 cytokine response
CD40L (Xq26.3)	T-cell costimulation of B cells	Escape from XCI; overexpression	Sustained antigen presentation

Conclusion

This report documents the first known coexistence of Rasmussen's encephalitis and Turner syndrome, extending the autoimmune neurological phenotype associated with X-chromosome monosomy. The association is unlikely to be coincidental and suggests a biologically plausible link mediated by haploinsufficiency of X-linked immune regulatory genes, resulting in impaired immune tolerance and facilitation of cytotoxic T-cell–driven cortical injury.

From a clinical perspective, this case underscores the need to consider Rasmussen's encephalitis in children with progressive focal epilepsy even in the presence of systemic chromosomal disorders, where diagnostic overshadowing may delay recognition. Serial electroclinical and radiological evaluation remains essential for timely diagnosis.

Importantly, while immunotherapy may transiently modulate disease activity, definitive seizure control is achieved only through hemispheric disconnection, and early surgical intervention should be strongly considered once progression is established.

Beyond its clinical relevance, this case provides a novel immunogenetic framework linking systemic chromosomal abnormalities to focal neuroinflammatory disease, highlighting the potential role of X-linked immune dysregulation in the pathogenesis of Rasmussen's encephalitis. Further studies are warranted to elucidate these mechanisms and refine patient selection for early definitive therapy.

Declarations

Funding:

No funding was received for this study.

Conflicts of Interest: The authors declare no conflicts of interest.

Ethics Approval: The study was conducted in accordance with institutional ethical standards.

Consent to Participate: Informed consent was obtained from the patient's guardians.

Consent for Publication: Consent for publication of clinical details and images was obtained.

Author Contribution

SM-Manuscript preparation and data collectionPC-Manuscript review,illustrationGCV-Article concept,manuscript review and case details acquisitionRM-EEG review,presurgical work up,Manuscript reviewAR-EEG review,presurgical work up,Manuscript review KK-Review and revision of manuscript

Acknowledgement

The authors acknowledge the contributions of the team at R Madhavan Nair Centre for Comprehensive Epilepsy Care,Trivandrum in the pre surgical work up and care.

References

1. Rasmussen T, Olszewski J, Lloyd-Smith D (1958) Focal seizures due to chronic localized encephalitis. Neurology 8(6):435–445
2. Bien CG, Bauer J, Deckwerth TL, Wiendl H, Deckert M, Wiestler OD et al (2002) Destruction of neurons by cytotoxic T cells in Rasmussen's encephalitis. N Engl J Med 347(16):1298–1306
3. Varadkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA et al (2014) Rasmussen's encephalitis: clinical features, pathobiology and treatment advances. Lancet Neurol 13(2):195–205
4. Schneider-Hohendorf T, Schwab N, Kunz P et al (2016) $CD8^+$ T-cell pathogenicity in Rasmussen's encephalitis. Nat Commun 7:11153
5. Granata T, Fusco L, Gobbi G, Freri E, Ragona F, Broggi G et al (2003) Rasmussen's encephalitis: early characteristics allow diagnosis. Neurology 60(3):422–425
6. Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M et al (2005) Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: European consensus statement. Brain 128(3):454–471

7. Delalande O, Bulteau C, Dellatolas G, Fohlen M, Jalin C, Buret J et al (2007) Vertical parasagittal hemispherotomy: long-term outcome in children. Neurosurgery 60(2 Suppl 1):ONS19–ONS32
8. Harris WB, Wirrell EC, Nickels KC, Wetjen NM, Meyer FB, Marsh WR (2019) Seizure outcomes after hemispherectomy for Rasmussen's encephalitis. J Neurosurg Pediatr 25(3):274–281
9. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO et al (2017) Clinical practice guidelines for Turner syndrome. Eur J Endocrinol 177(3):G1–G70
10. Mortensen KH, Cleemann L, Hjerrild BE, Nexo E, Locht H, Jeppesen EM et al (2009) Increased prevalence of autoimmunity in Turner syndrome. Clin Exp Immunol 156(2):205–210
11. Lleo A, Moroni L, Caliari L, Invernizzi P (2012) Autoimmunity and Turner's syndrome. Autoimmun Rev 11(6–7):A538–A543
12. Tangye SG, Al-Herz W, Bousfiha A et al (2018) Human inborn errors of immunity: update. Clin Exp Immunol 192(2):219–227
13. Syrett CM, Anguera MC (2019) X-linked gene dosage and autoimmunity. Trends Genet 35(5):339–350
14. Trolle C, Nielsen MM, Skakkebaek A et al (2021) Disruption of X-chromosome dosage in immune pathways in Turner syndrome. Clin Genet 100(4):450–459
15. Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T-cell development by FOXP3. Science 299(5609):1057–1061
16. Souyris M, Mejía JE, Chaumeil J, Guéry JC (2018) TLR7 escapes X-inactivation in immune cells. Proc Natl Acad Sci U S A 115(7):E1239–E1248
17. Linterman MA, Denton AE (2014) CD40L regulation and humoral immunity. Immunity 40(3):315–327
18. Ertan G, Aras Y et al (2012) Rasmussen's encephalitis and type 1 diabetes mellitus. J Child Neurol 27(10):1311–1314
19. Al-Qudah AA, Rawashdeh M, Al-Khatib SM et al (2017) Linear scleroderma and Rasmussen's encephalitis. Pediatr Neurol 70:78–81
20. Falip M, Carreño M, Miró J et al (2010) Anti-GAD65–associated epilepsy mimicking Rasmussen's syndrome. Epilepsia 51(6):1089–1092
21. Hamano SI, Tanaka M, Kobayashi K et al (2003) Hashimoto's encephalopathy mimicking Rasmussen's encephalitis. Brain Dev 25(5):346–349
22. Hart YM, Andermann F, Fish DR et al (1998) Rasmussen's syndrome: progressive autoimmune epileptic encephalitis. Brain 121(4):589–603

Figures

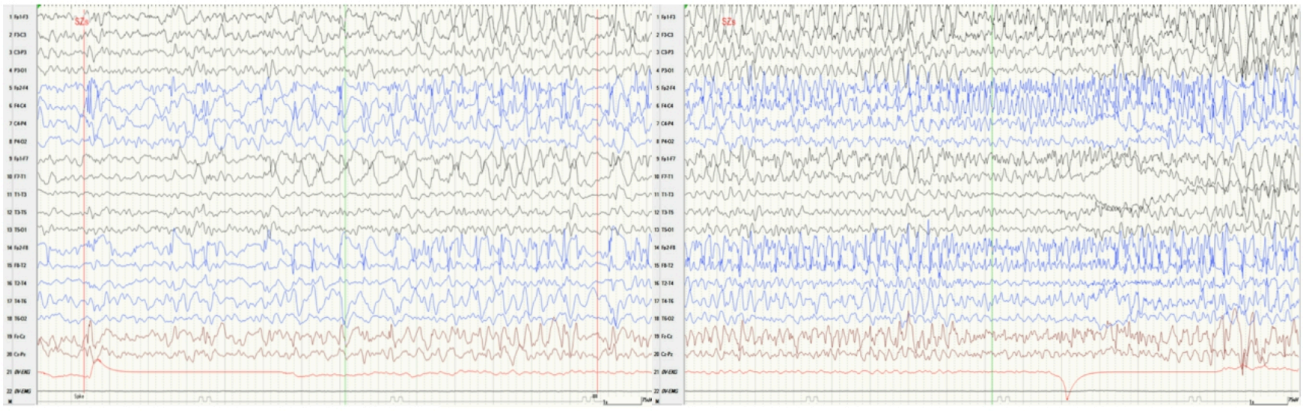


Figure 1

(Left)Right hemispheric slowing of EEG waveforms with frequent right frontal and fronto-central epileptiform discharges.

(Right) Low-voltage fast activity over the right fronto-central region.

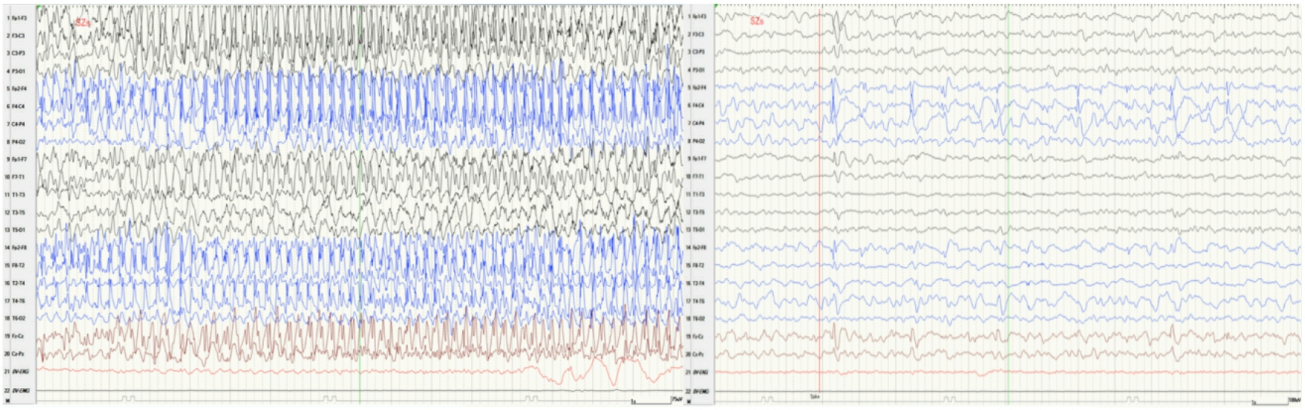


Figure 2

(Left) Ictal EEG:Rhythmic activity with intrahemispheric spread within the right hemisphere. (Right) Right fronto-central spike with phase reversal.

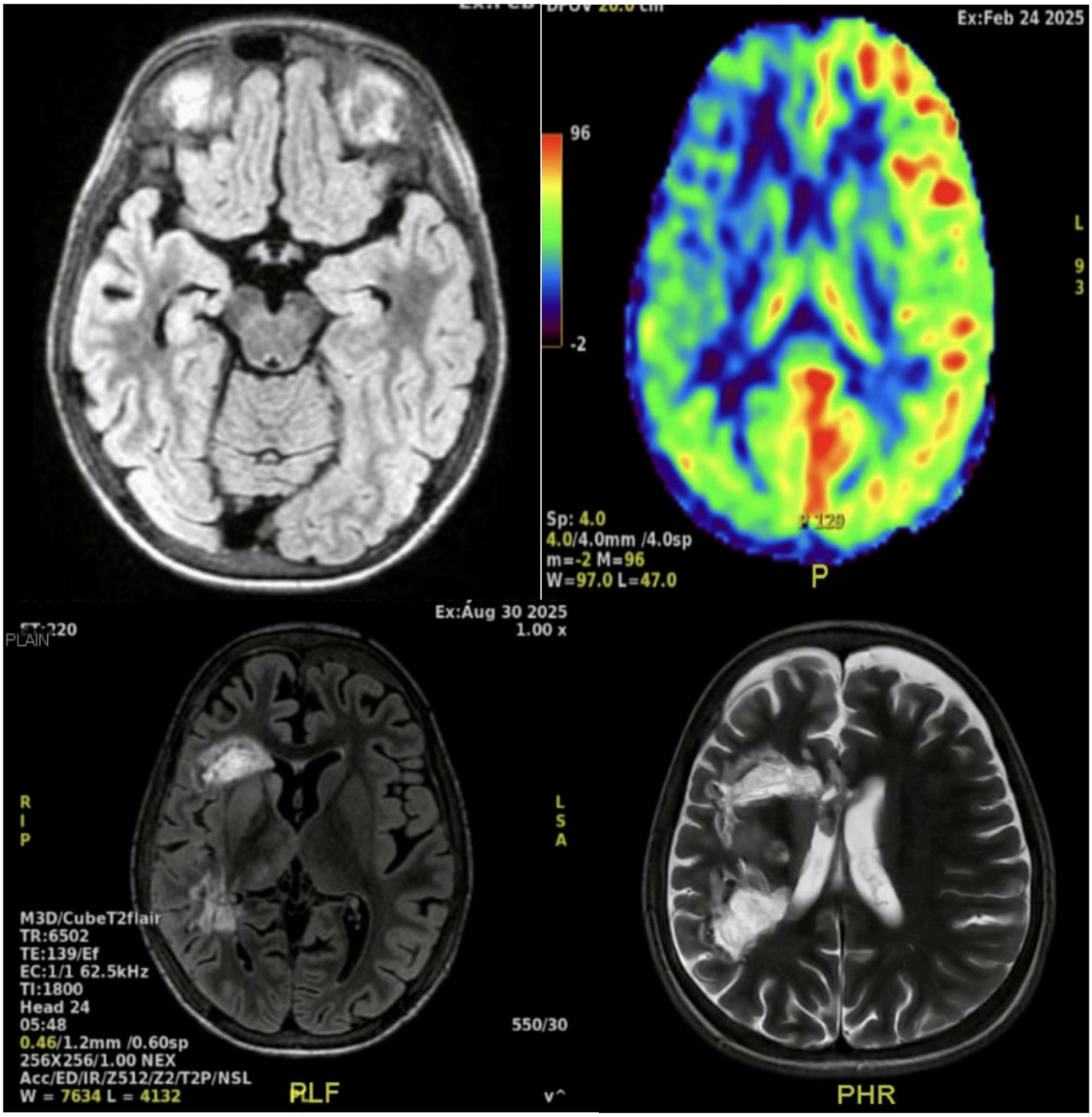


Figure 3

(Top-Left) Pre operative:Axial FLAIR sequence.

(Top-Right) Pre operative:Axial FLAIR sequence ASL(Arterial spin labelling)MRI

(Bottom-Left)Post-hemisphotomy MRI Axial FLAIR. (Bottom-Right) Post-procedure T2 Axial