Bridging Radiology and Pathology: ATRX Loss and T2-FLAIR Mismatch as Early Diagnostic and Prognostic Markers in Diffuse Gliomas

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Abstract

ATRX mutation and the T2-FLAIR mismatch sign have emerged as complementary molecular and imaging markers in diffuse gliomas. ATRX loss defines IDH-mutant astrocytoma at the molecular level, while the mismatch sign provides a non-invasive radiological clue with high specificity but limited sensitivity. Used together, they improve diagnostic precision, refine prognostic assessment, and guide individualized treatment planning.

Keywords: ATRX mutation, T2-FLAIR mismatch sign, Astrocytoma, Oligodendroglioma

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Introduction

Diffuse gliomas are a biologically heterogeneous group of primary brain tumours arising from glial cells, encompassing astrocytomas and oligodendrogliomas. The 2021 World Health Organization (WHO) classification has refined their diagnosis by integrating molecular and genetic alterations with histopathological assessment, thereby improving tumour characterization, prognostic stratification, and therapeutic guidance.[1] Globally, diffuse gliomas represent a major disease subset, accounting for approximately 42.8% of all primary neuroepithelial central nervous system (CNS) tumours.[2]

ATRX loss is strongly associated with IDH-mutant, 1p/19q-intact astrocytoma and closely correlates with the T2-FLAIR mismatch sign, an imaging marker highly specific for this subtype. In contrast, oligodendroglioma usually retain ATRX expression, harbour 1p/19q co-deletion, and rarely display the T2-FLAIR mismatch.

ATRX loss and the T2-FLAIR mismatch sign represent complementary molecular and imaging biomarkers that together bridge genetic alterations with radiological phenotype in diffuse gliomas. ATRX loss reflects disruptions in chromatin regulation and telomere maintenance, frequently via the alternative lengthening of telomeres (ALT) pathway, thereby delineating a distinct subset of astrocytic tumours. Conversely, the T2-FLAIR mismatch sign, characterized by uniform T2 hyperintensity with central FLAIR suppression, offers high specificity for IDH-mutant, 1p/19q non-codeleted astrocytomas and provides a non-invasive correlate of tumour architecture. When integrated, these markers improve diagnostic precision, guide biopsy planning, and offer prognostic insights; however, their utility is limited by variability in expression and imaging reliability, necessitating further validation. This review explores their interplay and independent occurrence, emphasizing their potential to refine early diagnosis and prognostication in gliomas.

Literature Review

ATRX loss and the T2-FLAIR mismatch sign have emerged as complementary molecular and imaging biomarkers in the updated WHO classification of adult gliomas. Together, they enhance the early diagnosis and prognostic evaluation of diffuse gliomas while facilitating distinction from oligodendrogliomas.[3] The T2-FLAIR mismatch sign defined by uniform T2 hyperintensity with central FLAIR suppression and a hyperintense peripheral rim demonstrates high specificity for IDH-mutant astrocytomas and serves as a reliable discriminator from glioblastoma in non-enhancing diffuse gliomas.[4]

Within this context, Jen et al., evaluated the reliability of the T2-FLAIR mismatch sign. In a cohort of 119 biopsy-confirmed IDH-mutant gliomas, the mismatch sign was found to be uncommon, but when present, was restricted to astrocytoma with either 1p/19q non-codeletion or ATRX mutation, and absent in oligodendroglioma. These findings demonstrated that the T2-FLAIR mismatch sign had high specificity for astrocytoma.[5]

However, despite its high specificity, the T2-FLAIR mismatch sign has notable limitations. Its sensitivity is consistently low; many IDH-mutant, 1p/19q non-codeleted astrocytoma will not display the sign. A study by Dagher et al., revealed that the definition of T2-FLAIR

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mismatch varied across studies, with "relaxed" or "partial" criteria (allowing for heterogeneity or partial mismatch) increasing sensitivity but reducing specificity, especially for 1p/19q status. Some studies have reported "false positives" in IDH-mutant, 1p/19q codeleted oligodendrogliomas and even in IDH-wildtype gliomas, particularly when less stringent criteria are used.[6]

Furthermore, technical factors such as MRI acquisition parameters and subjective interpretation also contribute to variability and potential misclassification. Additionally, the sign's performance in post-treatment settings is poorly characterized, and its association with clinical outcomes such as survival remains unproven. Finally, while histopathologic and molecular correlates have been suggested, these findings are based on small cohorts and require further validation.

In a recent retrospective series of 128 IDH-mutant gliomas, Jen et al., noted that the T2-FLAIR mismatch sign was absent in the earliest and smallest tumours. Instead, it emerges as the tumour matures, typically in rounded, sharply marginated, T2-homogeneous astrocytoma. As tumours enlarge, they lose T2 homogeneity and develop internal heterogeneity detectable with advanced MRI techniques. The T2-FLAIR mismatch sign emerges at a specific stage of tumour growth, may disappear after treatment, and can reappear with relapse. The study also highlights that "roundness" and T2 homogeneity are useful early imaging markers for astrocytoma's, helping to distinguish them from oligodendroglioma.[5]

Interestingly, novel studies have also shown that although the T2-FLAIR mismatch sign and ATRX loss are highly specific for IDH-mutant, 1p19q non-codeleted astrocytoma and are not seen in oligodendroglioma, other CNS tumours can mimic astrocytomas by showing ATRX loss and/or the T2-FLAIR mismatch sign, such as the paediatric-type MYB/MYBL1-altered diffuse astrocytoma and angiocentric gliomas that shows T2-FLAIR mismatch but typically lack ATRX loss. Dysembryoplastic neuroepithelial tumours (DNET) often display T2-FLAIR mismatch but retain ATRX and lack IDH mutation.[7]

In addition to this, ATRX loss in paediatric CNS tumours is a key diagnostic marker that distinguishes paediatric-type diffuse high-grade gliomas from adult-type gliomas and helps define molecular subgroups with distinct prognoses and therapeutic vulnerabilities. It is most common in midline and hemispheric paediatric high-grade gliomas. ATRX loss is diagnostically specific for paediatric-type diffuse astrocytomas and is mutually exclusive with 1p/19q codeletion, supporting integrated molecular classification.[8]

Keeping this in mind, we can safely say that the ATRX loss and the T2-FLAIR mismatch sign have broader clinical utility beyond astrocytomas. ATRX loss helps classify paediatric gliomas and glioneuronal tumours, while the T2-FLAIR mismatch sign can guide molecular testing and management in diverse CNS tumours.[9] Despite their specificity, these markers have limitations: ATRX loss is not unique to astrocytomas, and the T2-FLAIR mismatch sign may appear across tumour types. Thus, their use should be coupled with molecular testing and clinical context to mitigate misclassification.[10] Taken together, these insights underscore the evolving role of combined molecular–radiological approaches in glioma diagnostics and highlight the need for continued refinement of biomarkers that bridge imaging, pathology, and genomics to achieve more precise and personalized care.

Conclusion

ATRX loss and the T2-FLAIR mismatch sign capture distinct yet convergent aspects of diffuse glioma biology. While neither marker alone is sufficient, their integration enhances accuracy in distinguishing glioma subtypes and supports more personalized care. Future work should focus on standardizing imaging definitions and linking these markers to clinical outcomes, strengthening their role in precision neuro-oncology.

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References

1. Tariq Q, Ali EA, Anis SB, Yousaf I, Baig AN, Shamim MS. From Pixels to Prognosis: Artificial Intelligence and Machine Learning Models in Brain Tumour Mutation Prediction. J Pak Med Assoc. 2025;75:140–1.
2. Kim S, Son Y, Oh J, Kim S, Jang W, Lee S, et al. Global burden of brain and central nervous system cancer in 185 countries, and projections up to 2050: a population-based systematic analysis of GLOBOCAN 2022. J Neurooncol. 2025;175:673–85.
3. Adamou A, Beltsios ET, Papanagiotou P. The T2-FLAIR Mismatch Sign as an Imaging Indicator of IDH-Mutant, 1p/19q Non-Codeleted Lower Grade Gliomas: A Systematic Review and Diagnostic Accuracy Meta-Analysis. Diagnostics. 2021;11:1620.
4. Tauziède-Espariat A, Roux A, Benzakoun J, Kauv P, Tazi S, Métais A, et.al.loss in adult gliomas lacking H3 alterations or IDH mutations, an exceptional situation for exceptional diagnoses: the experience of Sainte-Anne hospital. Acta Neuropathologica Communications. 2025;13:131.
5. Jen JP, Patel M, Bowen M, Pohl U, Nagaraju S, Wykes V, et al. T2-FLAIR mismatch sign for diagnosis of 1p19q non-codeleted or ATRX mutant astrocytoma. Neuro-Oncol. 2021;23(Suppl 4):iv23.
6. Dagher SA, Lochner RH, Ozkara BB, Schomer DF, Wintermark M, Fuller GN, Ucisik FE. The T2-FLAIR mismatch sign in oncologic neuroradiology: History, current use, emerging data, and future directions. Neuroradiol J. 2024;37:441-53.
7. Kakkar A, Nambirajan A, Kaur K, Kumar A, Mallick S, Suri V, Sarkar

Table-1: Electrolyte and Fluid Challenges in AKI and CKD.

Parameter	Normal Handling	In AKI/CKD	Clinical Implication
Sodium (Na+)	Filtered (~25,000 mEq/day), 99% reabsorbed	Retention (↓GFR), or loss (diuretics/tubular dysfunction)	Hypertension, oedema, hyponatraemia
Potassium (K+)	Filtered & secreted in distal nephron	Reduced excretion, especially GFR < 30	Hyperkalemia (K+ > 5.5 arrhythmias)
Water	Regulated via ADH	Impaired free water clearance	hyponatraemia or volume overload in CKD stage 5
Urine Output	1–2 L/day	Often < 500 mL/day (stage 5), anuric in dialysis	Limits fluid administration; risk of pulmonary oedema
BP Regulation	Sodium balance and RAAS	Volume-sensitive hypertension common in CKD	ORS with high Na+ can worsen BP control

GFR-Glomerular Filtration Rate ADH-Anti-diuretic Hormone CKD-Chronic Kidney Disease RAAS-Renin-Angiotensin-Aldosterone System, ORS- Oral Rehydration Salt

clinical consequences. The clinical risks of fluid and electrolyte mismanagement are significant. For instance, in CKD stage 5 patients with negligible urine output, even small quantities of high-sodium or potassium-containing fluids can accumulate rapidly, increasing the risk of pulmonary oedema or life-threatening arrhythmias[8,9]. Similarly, patients with co-existing hypertension- a common comorbidity in CKD- are particularly vulnerable to excess sodium intake. Studies have shown that sodium restriction in CKD reduces blood pressure, proteinuria, and progression to dialysis.[10,11] Therefore, standard ORS formulations, which contain high sodium and potassium loads, may not only be inappropriate but also dangerous in this setting. These risks underscore the need for personalized ORS therapy, considering GFR, urine output, blood pressure control, and serum potassium levels.

Personalized ORS in Renal Dysfunction

There is an urgent need to move away from standardized rehydration strategies. A "one-size-fits-all" ORS is not only inappropriate but can be harmful in the presence of reduced glomerular filtration, oliguria, or electrolyte disturbances. The composition of ORS must be adjusted based on the stage of kidney disease, urine output, serum potassium levels, and comorbidities such as hypertension and heart failure.[12]

Table-2: Suggested Composition of Renal-Friendly ORS (By CKD Stage).

Component	WHO ORS	Stage 1–3 CKD	Stage 4 CKD	Stage 5 CKD (on or off dialysis)
Sodium (Na+)	75 mEq/L	50–70 mEq/L	40–60 mEq/L	30–50 mEq/L (with volume monitoring)
Potassium (K+)	20 mEq/L	10–15 mEq/L (monitor serum K+)	≤10 mEq/L (avoid if K+ > 5.5)	0–5 mEq/L (use K+-free ORS if anuric)
Glucose	75 mmol/L	50–75 mmol/L	50–60 mmol/L	50–60 mmol/L (avoid hyperglycaemia)
Chloride (Cl-)	65 mEq/L	45–60 mEq/L	40–50 mEq/L	35–45 mEq/L
Citrate	10 mmol/L	8–10 mmol/L	8–10 mmol/L	8–10 mmol/L (helps in mild acidosis)
Osmolarity	~245 mOsm/L	~220 mOsm/L	~200–210 mOsm/L	~180–200 mOsm/L
Recommended Intake	75–100 mL/kg/day	50–75 mL/kg/day (based on losses)	30–60 mL/kg/day (guided by output)	20–40 mL/kg/day (fluid-restricted)

In early-stage CKD (stages 1–3), the kidneys retain some capacity to regulate electrolyte and fluid balance.[7] However, even in these stages, patients may be salt-sensitive or on medications like RAAS inhibitors and diuretics that predispose them to hyperkalaemia or sodium losses. In stage 4 CKD (GFR < 30 mL/min), potassium retention becomes a more prominent issue, and patients often have volume management challenges. By stage 5 CKD (GFR < 15 mL/min or on dialysis), the kidneys are often unable to excrete even small loads of potassium or water, and many patients are anuric.[13] Consequently, both the composition and volume of ORS must be restricted and monitored closely.

To guide this individualized approach, Table 2 outlines suggested ORS modifications based on the stage of kidney disease. These values are not absolute, but serve as a practical guide to minimize risks while ensuring hydration in patients with renal impairment.

Clinical Application: When and How to Use Renal-Friendly ORS

Clinical scenarios where renal-friendly ORS is needed include vomiting, diarrhoea, poor oral intake, or post-dialysis fluid replacement in CKD patients. In stage 1–3 CKD, ORS with modest reductions in sodium and potassium may suffice. These patients still possess partial

Table-3: Summary of Evidence-Based Guidelines.

Parameter	Recommendation
Sodium (Na+)	Limit to 30–50 mEq/L in stage 4–5 CKD and hypertensives
Potassium (K+)	<10 mEq/L in CKD stage 4; avoid if serum K+ > 5.5 mEq/L or anuria
Total Volume of ORS	Match to fluid allowance; 20–40 mL/kg/day in stage 5 CKD
Use of Commercial ORS	Avoid unless low-K+, low-Na+ variant is available
BP and weight monitoring	Daily BP, weight, and symptom monitoring essential
When to Avoid ORS	Anuria, hyperkalaemia > 5.5, pulmonary oedema, uncontrolled hypertension

renal compensatory mechanisms and may benefit from hydration during illness or in hot climates.[9] Monitoring of blood pressure and serum potassium is advisable. In stage 4 CKD, ORS should be used more cautiously. Potassium should not exceed 10 mEq/L, and sodium should remain under 60 mEq/L, particularly in oedematous or hypertensive individuals. The volume of ORS should be guided by the patient's daily urine output and weight change. In stage 5 CKD, whether on or off dialysis, ORS must be used only when necessary, and with extreme care. Most such patients are oliguric or anuric. Here, potassium-containing solutions should be avoided completely, and sodium restricted to <50 mEq/L. Fluid intake must be calculated precisely: total intake = urine output (if any) + insensible losses (~400–600 mL/day). Daily weight and blood pressure monitoring should guide ongoing adjustments.

To help clinicians apply these principles effectively, Table 3 outlines evidence-based recommendations for prescribing ORS in patients with renal dysfunction. These recommendations are based on pathophysiological principles, practical experience, and current best practices in nephrology. While randomized controlled trials in this domain are scarce, several observational studies and guideline reviews reinforce the need for salt and potassium restriction in advanced CKD, especially in oliguric or hypertensive patients. Furthermore, in CKD patients with coexisting cardiovascular disease, even small fluid shifts due to inappropriate ORS can trigger decompensation.[12] Therefore, every decision to use ORS in renal patients must be individualized and justified by clinical need.

Conclusion

Standard ORS formulations may worsen hypertension, hyperkalaemia, and fluid overload in CKD, especially in stages 4 and 5. A renal-friendly ORS must be tailored based on GFR, serum potassium, blood pressure, and urine output. Sodium and potassium content must be tightly regulated, and volume administration should be individualized. Low-potassium, low-sodium, and reduced-osmolarity ORS solutions- along with close clinical monitoring- can safely support hydration in this vulnerable population.

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References

1. Buccigrossi V, Lo Vecchio A, Bruzzese E, Russo C, Marano A, Terranova S, Cioffi V, Guarino A. Potency of Oral Rehydration Solution in Inducing Fluid Absorption is Related to Glucose Concentration. Sci Rep. 2020;10:7803. doi: 10.1038/s41598-020-64818-3. PMID: 32385331; PMCID: PMC7210290.
2. World Health Organization. Implementing the New Recommendations on the Clinical Management of Diarrhoea: Guidelines for Policy Makers and Programme Managers. Geneva: World Health Organization; 2006.
3. Borrelli S, Provenzano M, Gagliardi I, Michael A, Liberti ME, De Nicola L, Conte G, Garofalo C, Andreucci M. Sodium Intake and Chronic Kidney Disease. Int J Mol Sci. 2020;21:4744. doi: 10.3390/ijms21134744. PMID: 32635265; PMCID: PMC7369961.
4. Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol. 2019;32:499-516.
5. Kaufman DP, Basit H, Knohl SJ. Physiology, Glomerular Filtration Rate. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500032/
6. Kovesdy CP. Significance of hypo- and hypernatremia in chronic kidney disease. Nephrol Dial Transplant. 2012;27:891-8.
7. Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. Kidney Dis (Basel). 2017;3:136-148.
8. Martin K, Tan SJ, Toussaint ND. Total Body Sodium Balance in Chronic Kidney Disease. Int J Nephrol. 2021:7562357. doi: 10.1155/2021/7562357. PMID: 34603798; PMCID: PMC8481067.
9. Yamada S, Inaba M. Potassium Metabolism and Management in Patients with CKD. Nutrients. 2021;13:1751. doi: 10.3390/nu13061751. PMID: 34063969; PMCID: PMC8224083.
10. McMahon EJ, Campbell KL, Bauer JD, Mudge DW, Kelly JT. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev. 2021;6:CD010070.
11. Borrelli S, Provenzano M, Gagliardi I, Michael A, Liberti ME, De Nicola L, Conte G, Garofalo C, Andreucci M. Sodium Intake and Chronic Kidney Disease. Int J Mol Sci. 2020;21:4744. doi: 10.3390/ijms21134744. PMID: 32635265; PMCID: PMC7369961.
12. Al-Naher A, Wright D, Devonald MAJ, Pirmohamed M. Renal function monitoring in heart failure - what is the optimal frequency? A narrative review. Br J Clin Pharmacol. 2018;84:5-17.
13. Rout P, Aslam A. End-Stage Renal Disease. [Updated 2025 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499861/