Acute Lymphoblastic Leukemia with Central Nervous System Relapse: Case series of unusual presentation

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ABSTRACT:

Central nervous system (CNS) relapse in acute lymphoblastic leukemia (ALL) was and still is a major site for relapse that adversely affects the cure rate. This is a retrospective case series, the characteristics of three diagnosed with early and late, isolated CNS and combined B-ALL relapse after initial frontline therapy were reported. The present study throws the shades on three of the rare and unusual presentation of relapsed CNS lymphoblastic leukemia among children, with challenges in early diagnosis and affirmation of the importance of appropriate CNS directed therapy.

Keywords: *Acute lymphoblastic leukemia; Central nervous system; Relapse; Children; Case series*

Introduction:

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer that represents a success tale of improved cure rates from ~ 10% in the 1960s reaching more than 90% with the currently adopted treatment regimens ***[Hunger & Mullighan 2015].*** This previous cure gap in the early decades has been much associated with the absence of incorporated central nervous system (CNS)-directed therapy in the earliest treatment protocols, with 80% of all patients' relapses being in the CNS. Thus, a major contributor to the excellent cure rates achieved currently was the use of CNS-directed therapy in the 1960s, including intrathecal (IT) chemotherapy, high-dose methotrexate (HD-MTX) and/ or cytarabine (HD-AraC), with or without CNS irradiation ***[Simone 1973 & Vora et al., 2016].*** Data from previous autopsy studies showed that the majority of leukemia patients developed CNS disease during their course of treatment ***[Price & Johnson 1973].*** For which, regardless of the initial CNS status, all patients receive IT prophylactic chemotherapy during their treatment protocol ***[Cheung et al., 2018].*** With this integrated frontline treatment regimens, the overall risk of CNS relapse has now declined to less than 5%; however, 30–40% of all relapses still occur in the CNS ***[Bhojwani & Pui 2013].*** Risk factors at initial diagnosis that predisposes to CNS relapse include; T-ALL immune-phenotype (IPT), ALL with adverse cytogenetics as [t(9;22) and t(1,19) & KMT2A rearrangement], hyperleukocytosis with white blood cell count (WBC) above 100 x 10^9/L, slow early response and overt CNS disease ***[Pui & Howard 2008].*** Patients with CNS relapse who were shown to demonstrate the lowest survival outcomes, were those early relapsing patients with a period of remission of less than 18 months from initial diagnosis, and those with previous history of cranial irradiation. Fortunately, at time of CNS relapse, most patients respond well to relapse therapy, achieving a 2nd CNS remission ***[Barredo et al., 2006].*** However, in some patients, leukemia is resistant to the conventional 2nd line therapy that includes ITT twice weekly and intensified block, with the ultimate need for radiation therapy as well as novel agents as; the chimeric antigen receptor (CAR)-modified T-cell therapy, which demonstrated in the recent trials to be highly effective in clearing CNS leukemic cells, yet on the expenses of an increased risk of both radiation therapy and CAR T-associated neurotoxicity ***[Pasquini et al., 2020].*** This raises the importance of accurate diagnosis of CNS leukemia initially and at time of relapse, as well as accurately measured response assessment to ensure adequately delivered therapy avoiding unintended toxicities. The gold standard in assessing leukemia CNS involvement is the accurate detection of blast cells in the cerebrospinal fluid (CSF) after lumbar puncture ***[Bürger et al., 2003].*** The CNS status definition is determined by the quantification of the WBCs in the CSF along with microscopic examination of a cytocentrifuged CSF sample to identify leukemic blasts, which is then used to assign patients to CNS1, CNS2 or CNS3 status ***[Smith et al., 1996],*** also CNS3 status is given to patients with clinical or radiological evidence of CNS-leukemia, irrespective of CSF findings e.g. 7th cranial nerve palsies, or other neurological symptoms that can be associated with CNS-imaging findings ***[Thastrup et al., 2022].*** However, CNS leukemia can have a diverse presentation which needs strict caution and attention for appropriate diagnosis; we are reporting series of patients diagnosed with early and late, isolated CNS; as well as; combined B-ALL relapse after initial frontline therapy according to Total XV protocol, receiving ALL-REZ BFM 2002 at time of relapse diagnosis.

Ethical consideration

(1) An approval of the Ethical Committee of Faculty of Medicine, Ain Shams University under acceptance number FMASU R31/ 2024 was obtained.
(2) An Informed consent was taken from parents or care givers before getting involved in study.
(3) Financial disclosure: The author received no financial support for the research.
(4) The authors declared no potential conflicts of interest with respect to the research and publication of the research.
(5) The data of the study are confidential, and the patient has the right to keep it.
(6) The patient has the right to refuse.

Methods:

This is a retrospective case series covering the period from 1st August 2020 to 31st December 2023. The characteristics of three patients who was diagnosed and was following at Pediatric Hematology Oncology and BMT Department, Ain Shams University, Cairo, Egypt.

Inclusion criteria:

- Age: >1-<18 yrs.
- Diagnosis: CNS ALL relapse.
- Isolated & Combined relapse.

Exclusion Criteria:

- Patients with de no Vo leukemia & CNS disease.

The clinical characteristics: Data were collected from the electronic medical records of the hospital, as well as from the patient's paper archiving system.

The Laboratory analysis: Data was collected from the electronic medical records including the immunophenotypic analysis which was performed by eight-color flow cytometry (FCM). Interphase fluorescence in situ hybridization (FISH) was performed using dual-color dual fusion probes for BCR: ABL1 and PBX1:TCF3, whereas KMT2A gene rearrangement was assessed using a break-apart probe. Karyotyping was performed using the conventional GTG-banding technique.

Imaging: Data of magnetic resonant imaging (MRI) brain (GE Logia p7 ultrasound machine (GE Healthcare, Waukesha, Wisconsin, USA) with high resolution linear probe 7-12 MHz was collected.

Treatment protocol: All patients were treated with front line chemotherapy according to the total XV protocol at their initial diagnosis, receiving 6 weeks of induction therapy (prednisone, doxorubicin, E.coli L-aspar, vincristine, cyclophosphamide, cytarabine, 6 mercaptopurine, as well as ITT) followed by FCM MRD at end of induction, then consolidation by HDMTX (from 2.5-5gm/m^3/ dose over 24 hrs. according to the patients' risk), 6 Mercaptopurine and ITT then 120 weeks of continuation therapy with two intensified reinduction cycles at weeks7-9 and weeks 17-19. At time of relapse all patients were enrolled to the ALL-REZ BFM 2002 receiving dexamethasone pre-phase, remission induction intensive blocks with or without radiation therapy and HSCT with variable number of ITT according to CNS status at time of relapse.

Case (1):

A twelve years old, Chadian male patient, was initially diagnosed at our institute with B-ALL after his presentation with high grade fever, generalized boney aches and bilateral knee arthritis. His initial peripheral blood study showed a high total leucocytic count (TLC) ($74x10^3$/l), low hemoglobin (Hb) (5.3 g/dl) and low platelet count ($7x10^3$) with 40% blasts. Needle bone marrow aspiration (BMA) and FCM studies confirmed presence of 80% blasts expressing B cell lymphoid markers: CD19 (91%), CD76a (96%) positive as well as positive expression of HLA-DR (96%) and being negative for myeloid and T cell lymphoid markers. Conventional cytogenetic and FISH were negative for Philadelphia translocation, KMT2A rearrangement as well as translocation 1,19. Initial CSF cytology showed no evidence of malignant infiltration. The patient started total VX protocol standard risk arm, with BMA end of induction showed complete remission with FCM minimal residual disease (MRD) of 0.0001%. After which upon patient's request was referred

back to Chad for completing his 120 weeks of continuation therapy.

The patient was later presented to us with bilateral abducent nerve palsy in the form of alternating convergent squint associated with headache and neck rigidity of one month duration. MRI brain was performed showing acute supra-tentorial and infra-tentorial hydrocephalic changes with mild tonsillar herniation (Figure 1). CSF cytology showed 30 lymphocytes which by flow cytometry shown to be reactive T lymphocytes expressing T-cell markers CD2, CD3, CD5 as well as CD7 with BMA showed 1 % blasts with MRD 0.03%. The patient inserted ventriculo-peritoneal (V-P) shunt with complete recovery of cranial nerve palsy with resuming back of his chemotherapy which he reached week 22 continuation, however the patient reported missing all ITT since the start of the continuation therapy which were planned to be compensated. Fifty-two weeks later the patient presented to the ER with severe headache, vomiting as well as blurring of his vision; fundus examination showed well defined optic disc margins and CSF cytology showed 10 lymphocytes. MRI brain showed right temporal large space occupying lesion (SOL) measuring 2x3.3x3.7 cm. (Figure 1). The patient underwent right tempro-parietal craniotomy, total tumorectomy with the gross appearance of the mass infiltrating the surrounding brain parenchyma with ill-defined boundaries. Pathological examination proved the lymphoid neoplastic nature of the mass which was strongly positive for terminal deoxynucleotidyl transferase (TDT) and KI 67. His BMA showed 1 % blasts with MRD 0.02%

The patient showed postoperative full recovery without any complication and was determined as early isolated CNS relapse; and was shifted to the BFM ALL 2002 Relapse protocol. Evaluation after the pre-phase and 1st induction block, by BMA showed 1 % blasts with MRD 0.05%. Unfortunately, after starting the 2nd induction block of therapy; the patient developed acute encephalopathy with Glasgow coma scale 3, Urgent computerized tomography (CT) brain scan showed no evidence of any residual enhancing mass, shortly after the patient was intubated and admitted to the intensive care unit and died 72 hours later.

Case (2)

Eleven years old, Egyptian female patient diagnosed as B-ALL at our institute after presenting with persistent fever and joint pain and misdiagnosis as rheumatoid arthritis for which was treated with systemic low dose MTX for twelve months without improvement. Her peripheral blood counts on presentation showed normal TLC (6 10^3/l), low Hb (4 g/dl) and low platelet count (46x10^3). Initial BMA and FCM showed 95 % blast cells expressing CD19=96%, CD20=38 %, CD79a=99%, CD58=96% with negativity to T lymphoid markers and myeloid markers with initial no evidence of malignant infiltration was found in CSF. Initial karyotyping was 46, XX, with negative FISH results for t1,19, t9,22, as well as KMT2A rearrangement. The patient started total VX protocol with BM end of induction showed MRD 0.005%. Accordingly, patients continued her therapy as low risk (LR) B-ALL receiving, consolidation 4 cycles HD-MTX on 2.5gm/m^2 with ITT, followed by the maintenance therapy, with BM performed after therapy completion confirming complete remission status with negative FCM MRD.

Two months following end of therapy the patient started developing headaches with blurring of vision, her fundus examination revealed grade 4 papilledema and MRI brain showed mild accentuated leptomeningeal enhancement suspicious of CNS leukemic infiltration involving optic nerves and posterior fossa, as well as bilateral ethmoid, maxillary and sphenoidal sinusitis (Figure 2) and MRI spine revealed linear enhancement along cauda equine nerve roots. CSF examination revealed elevated opening pressure (45 cm H_2O) with 600 atypical cells showing B-ALL IPT of the same initial clone. BM examination confirmed 2% blasts with MRD 0.002%. The patient was considered as early isolated CNS relapse, started BFM ALL 2002 Relapse protocol and received dexamethasone pre-phase with ITT, with rapid CSF clearance as well as, resolution of symptoms of increased ICP. BM evaluation after two intensive induction blocks 1 % blasts in aspirate

with undetectable MRD for which the patient currently receiving intensive blocks of chemotherapy to be followed by cranial radiation and maintenance therapy.

Case (3):

Seven years old, Egyptian male patient, diagnosed as B-ALL after developed multiple ecchymosis all over his body with initial peripheral blood film of high TLC (40x 10^3/l), low Hb (4 g/dl), low platelet count (14x10^3/l) with 81 % blasts. His BMA showed 98 % blast cells, FCM confirmed blast cells positive CD 19 =99%, CD 79a =95%, HLA-DR=67% with negativity to T lymphoid markers and myeloid markers, and no evidence of malignant infiltration was found in CSF cytology. His initial karyotyping was 46, XY with negative FISH for t1,19, KMT2A rearrangement and t9,22. Accordingly the patient started total VX protocol. BM end of induction showed nondetectable FCM MRD, accordingly the patient received his treatment as LR ALL with end of therapy bone marrow aspiration confirming CR and FCM MRD of 0.007%.

Four years after the patient's initial diagnosis, the patient developed a progressive headache with blurring of vision that progressed to diminution of vision. His fundus examination revealed grade 2 papilledema, with visual acuity assessment revealing bilateral light perception. MRI brain showed diffuse thickening of both optic nerve sheathes with signal alteration of both optic nerves and to lesser extent 7^{th} ,8^{th}, and 5^{th} nerves bilaterally, picture suggestive of leukemic infiltrates (Figure 3). CSF cytology revealed 8280 cells with IPT of B-ALL resembling initial clone. BM studies confirmed 14% blasts in aspiration and MRD 12%. Accordingly, the patient was diagnosed with late combined medullary and CNS relapse and started BFM ALL 2002 Relapse protocol, follow up fundus examination revealed bilateral optic atrophy. Evaluation after induction blocks of therapy by bone marrow aspiration showed 2 % blasts with MRD 0.003%, MRI brain showed regression of previous optic nerve changes, yet visual acuity assessment was same findings. The patient is currently well and alive completing relapse regimen treatment.

Discussion:

Pediatric ALL achieves with the currently running national and international chemotherapy-based treatment; protocols ˷80–90% cure rates ***[Pui & Evans 2006].*** One in each five children relapses during the course of the disease, which has been associated with poorer outcomes ***[Pui & Evans 2006].*** Accurate diagnosis and treatment of CNS leukemia represents a challenging dilemma, which is detected in about 3–5% of patients at initial diagnosis and 30–40% of patients at relapse ***[Pui & Howard 2008].***

Starting with the risk for CNS relapse, among our series, the three patients were expressing B-ALL IPT, high initial TLC in 2 cases, with no evidence for CNS involvement initially nor the presence of adverse cytogenetic, and case 1 experienced interrupted ITT during maintenance therapy. In contrast to our data, ALL risk groups for later CNS relapse includes T rather than B IPT, patients with initial adverse cytogenetics, hyperleukocytosis, as well as patients initially presenting with CNS3 status ***[Pui & Howard 2008]*** and without appropriate CNS prophylaxis therapy with the frontline treatment, more than 50% of those children develop CNS relapse ***[Evans et al., 1970].*** It is also worth mentioning that patients with traumatic lumbar puncture at diagnosis (≥ 10 red blood cells per µL) with the blasts are associated with lower event free survival (EFS) ***[Gajjar et al., 2000].***

Acknowledging those upfront initial risk, high risk patients are treated according to risk adapted frontline regimens aiming at decreasing the risk of CNS relapse including receiving prophylactic cranial irradiation and introducing specific CNS-directed prophylaxis earlier, as substituting dexamethasone for prednisone, which is associated with lower CNS and systemic relapse rates in pediatric and adult ALL patients ***[Mitchell et al., 2005].*** However, cranial irradiation can induce long-term neurocognitive defects, for which therapeutic regimens have been modified to decrease or omit cranial radiation, substituting it with intra-thecal and systemic chemotherapy ***[Gay et al., 1989].*** A large retrospective analysis of CNS relapse

reported no difference in relapse rates between patients who received and did not receive cranial irradiation and also demonstrated that with effective risk-adjusted systemic chemotherapy and intrathecal therapy initiated at diagnosis, cranial irradiation can safely be omitted from CNS-directed treatment without compromising overall survival in all newly diagnosed ALL patients. ***[Pui et al., 2009]***

Along with high levels of suspicion, diagnosis of CNS relapse resets upon clinical, laboratory as well as imaging finding. In our series the three patients presenting complaints ranged from symptoms of increased ICP, as well as cranial nerve involvement. In a previous series of adult patients with CNS leukemia at initial diagnosis reporting fourteen different patients ***[Liu et al., 2017],*** Most of patients suffered nonspecific symptoms, including convulsions, headache, vomiting and altered mental status. Few patients experienced focal neurological deficits, such as weakness and vision diminution. Prodromal symptoms, including fever, night sweat and weight loss, were also commonly reported. Most reports focus on the presence of blast cells in the CSF for diagnosis of CNS leukemia and CNS leukemic relapse, and/or the development of 7th cranial nerve palsy, although rarely recognized. As there is rarity in cranial nerve palsy due to CNS leukemia, this rarity undoubtedly accounts for the lack of information on clinical features and treatment outcome for patients with cranial nerve palsy at diagnosis ***[Ingram et al., 1991].***

In a report describing forty-five patients with either ALL or non-Hodgkin lymphoma (NHL) who had cranial nerve palsy either at diagnosis or at relapse of their disease, the 7th cranial nerve was the most frequently involved (15 of 22 cases) followed by cranial nerves III (six of 22) and VI (four of 22); unilateral disease was more common than bilateral disease (ratio, 3.4: l). One child with paraspinal NHL, and bilateral CNP progressed to paraplegia and only seven children had blast cells in their CSF ***[Ingram et al., 1991].*** In contrast to the published data all the three patients in our series had bilateral cranial nerve involvement affecting the optic nerve in case 2 and 3 with marked drop of visual acuity in case 3, while case 1 was presenting uniquely with bilateral abducent cranial nerve palsy. For relapsed ALL presenting with neurologic deficit it can be attributed to brain parenchymal masses with scarcity of reports of the unusual presentation.

Unlike ALL, extramedullary leukemic masses are relatively common finding in newly diagnosed children with acute myeloid leukemia (AML) either as isolated or combined with medullary involvement which is known as myeloid sarcoma. Among interesting case reports ***Meena et al 2017*** described acute presentation of a 7-year-old male presenting initially with fever, bilateral lower limb weakness, progressing into seizure and impaired urinary and fecal continence that were diagnosed 2.5 months later as AML with intracranial and paravertebral masses ***[Meena et al., 2018].***

Although the best treatment approach for relapsed ALL remains uncertain, there is agreement that when relapse occurs early, leukemia-free survival remains dismal; most children still die despite aggressive chemoradiotherapy approaches, including transplantation, and novel salvage regimens are needed. The timing of relapse has emerged as the most significant predictor of outcome and the most important factor for a relapse is the duration of the first remission; early relapse has worse prognoses than late relapse ***[Rheingold et al., 2019].***

Conclusion:

The present study throws the shades on three of the rare and unusual presentations of relapsed CNS lymphoblastic leukemia among children. Highlighting the challenges in early diagnosis given inconsistent clinical picture with the published previous reports and reinforce the affirmation of what was previously concluded about the importance of appropriate CNS directed therapy.

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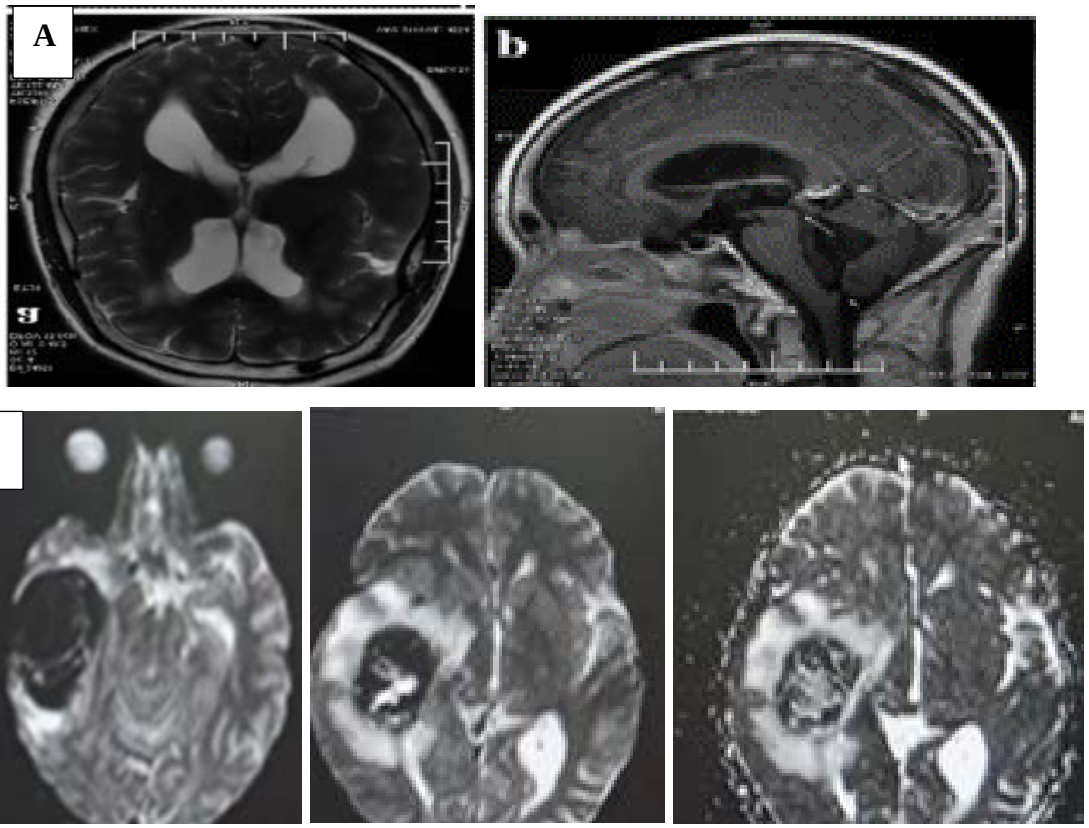

Figure 1: Magnetic resonant imaging (MRI) brain of case 1 pre-and post-operative. A: MRI brain imaging (preoperative) showing acute supra-tentorial and infra-tentorial hydrocephalic changes with mild tonsillar herniation. B: right temporal large space occupying lesion with two components one has a dural base eliciting intermediate to low T1 signal, intermediate T2 and FLAIR signal with post contrast enhancement measuring 2x3.3x3.7 cm, while the medial aspect shows hematoma and surrounding vasogenic brain edema.

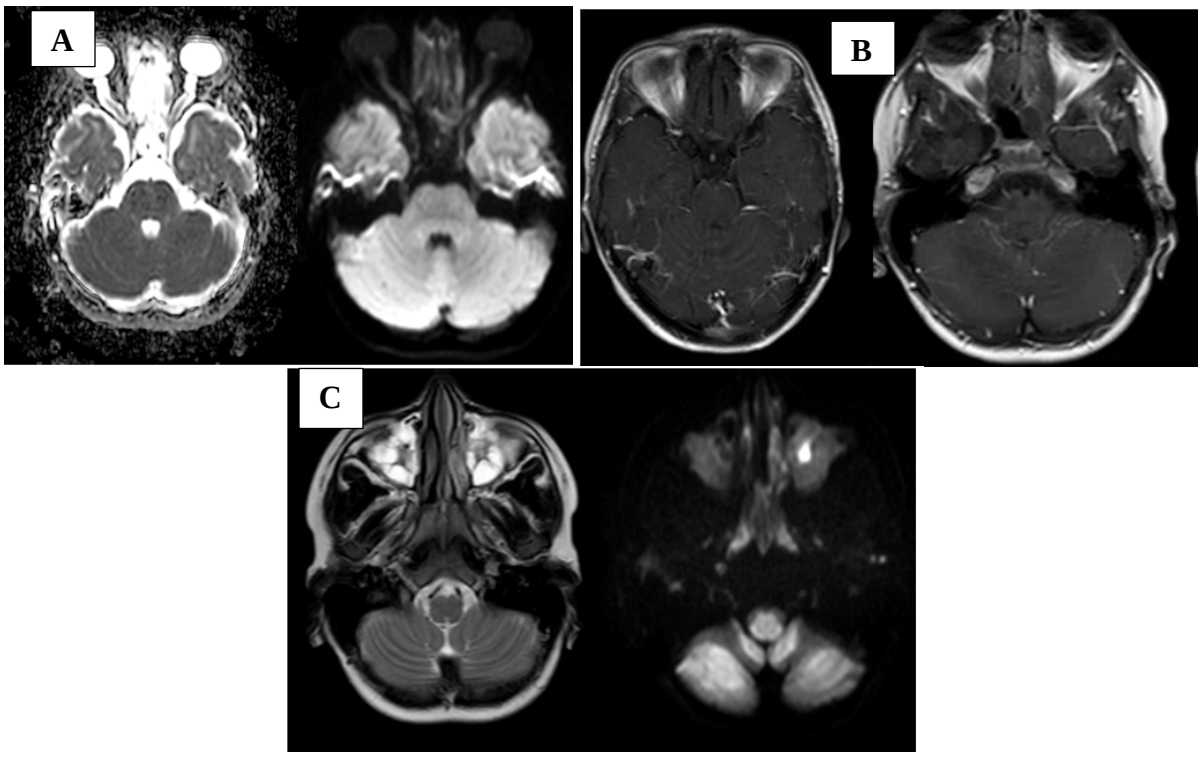

Figure 2: Magnetic resonant imaging (MRI) brain of case 2. A: DW restriction affects both optic nerves. B: Mild accentuated leptomeningeal enhancement along posterior fossa especially cerebellar fossa and to lesser degree cerebral hemispheres. C: bilateral ethmoid, maxillary and sphenoid sinusitis with left maxillary central DW restricted focus suggestive of pus locule

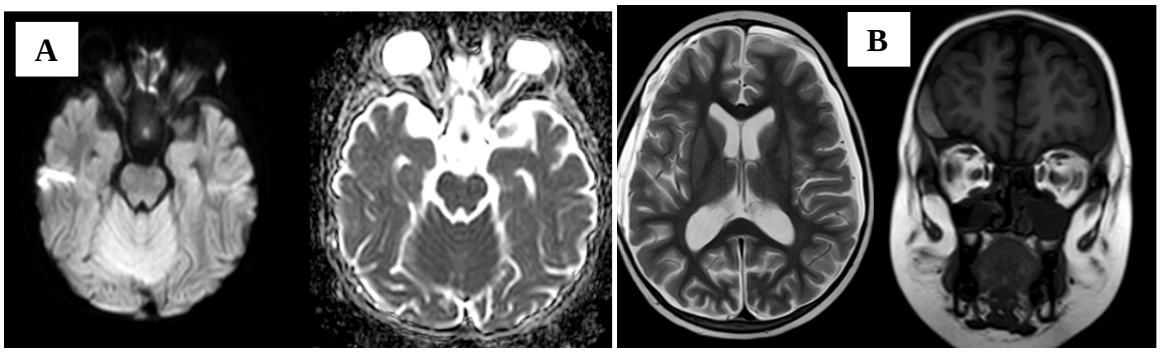

Figure 3: Magnetic resonant imaging (MRI) brain of case 2. A: There is diffuse thickening of the optic nerves sheathes bilaterally with related DW restriction with signal alteration of both optic nerves and flattening of both optic discs. B: Mild right parietal localized subdural collection with iso to high signal intensity on T2 and FLAIR and low signal intensity on T1W1 suggestive of subacute subdural hematoma