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Case Report

Fatal Acute Encephalopathy Associated with Influenza A Infection in a Pediatric Patient with Low-Grade Pediatric Glioma: A Case Report and Review of the Literature

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Abstract

Neurologic complications are reported in up to 18% of children hospitalized with influenza, especially in those with underlying comorbidities. We report the case of a 1-year-old boy affected by a low-grade neuroglial neoplasm of the posterior cranial fossa, who developed during the winter season, while on chemotherapy, an Influenza-Associated-Encephalopathy (IAE), which rapidly led to death. The patient presented with respiratory symptoms followed, after three days, by seizures and progressive reduction of consciousness till coma. A nasopharyngeal swab resulted positive for Influenza A while all other laboratory and radiological exams were not significant. Treatment was based on Intravenous Immunoglobulins (IVIG), corticosteroids, and oseltamivir, which was started six days following hospitalization, but no improvement was observed. The patient died after twelve days from symptom onset. In children with encephalitis or acute onset of neurological symptoms, Influenza must be considered in the differential diagnosis. This case points out that seasonal vaccination for influenza may help prevent this rare but fatal complication in immunocompromised patients.

Keywords: Influenza; Influenza-Associated-Encephalopathy; Children; Neurologic Complications; Pediatric Neuroglial Neoplasm

Abbreviations: IANCs: Influenza-Associated Neurological Complications; IAE: Influenza-Associated Encephalitis; ANE: Acute Necrotizing Encephalopathy; PICU: Pediatric Intensive Care Unit; N/A: Not Available

Introduction

Influenza is one of the most frequent causes of pediatric respiratory disease resulting every year in roughly 870.000 hospitalizations in children younger than 5 years of age [1]. The infection is usually self-limiting, although some complications can develop, especially in pediatric and elderly populations, and immunocompromised patients. The incidence of influenza-

associated pediatric deaths reported in the US each year is 0.15 per 100.000 children and it is highest among children aged <6 months (0.66 per 100.000) [2]. Notably, according to the available literature, influenza-associated neurologic complications are not rare in children hospitalized with influenza, occurring in up to 18% of this population. [3 - 11]. Children account for most neurologic complications, which are associated with higher morbidity and mortality [12, 13]. A previously underlying condition is associated with an increased risk of neurological complications and a worse prognosis [4, 14, 15]. Reported neurological manifestations of influenza include febrile seizures, non-febrile seizures, Encephalopathy/Encephalitis (IAE), Guillain-Barré Syndrome, stroke, and myelitis. Antiviral agents such as neuraminidase inhibitors, and immunomodulatory treatments (corticosteroids, intravenous immunoglobulin), are currently administered but the evidence of their efficacy is limited. Nowadays, there are no available biomarkers to predict outcomes [16, 17]. We report a unique case of a fatal influenza-associated neurological complication in a neuro-oncologic child admitted to a tertiary pediatric Hematology Oncology Center. We also did a review of the literature concerning this topic.

Case report

A 1-7-year-old boy presented with torticollis with left neck deviation and ataxia. The craniocervical RMI showed a cervical-medullary lesion involving the medulla oblongata, the cervical cord down to C3, and the left cerebellar vermis. Due to the infiltrative features of the tumor, lacking a clear cleavage plan, a subtotal tumor removal was performed with the use of intraoperative neurophysiological monitoring. Post-operatively the patient presented a left arm hyposthenia and some dysphagia, which both gradually improved with physiotherapy. No tracheostomy was required. The histological diagnosis was consistent with a low-grade neuroglial neoplasm with desmoplasia, BRAF gene mutated. Based on the small residual tumor and the benign features of the tumor, no adjuvant therapy was considered at this stage and the child was followed up with a control MRI initially every 3 months. After 11 months from intervention, the MRI showed evidence of progression. Therefore, chemotherapy according to the SIOP LGG 2004 protocol was started in June [18]; standard induction consisted of ten weekly doses of Vincristine (VCR) 1.5 mg/m2 and four single doses of carboplatin (CBDCA) 550 mg/m2 at 3-week intervals followed by three cycles of simultaneous VC at 4-week intervals. Importantly, the patient did not receive the annual influenza vaccination for the following fall-winter season. After 10 days from the eighth line of vincristine/carboplatin, in the month of January, the patient presented to the emergency department of a peripheral hospital with a three-day history of cough and fever. On examination he was in good clinical condition, the only significant finding was the presence of crackles at the base of the right lung. The lab tests showed hemoglobin 111 g/L, platelets 188 x109/L, leucocytes 1,08 x 109/L, polymorphonucleated 0,79 x 109/L, Reactive C Protein (CPR) 27 mg/L [NV <5 mg/L], Lactic Dehydrogenase (LDH) 579 U/L [NV 120-300 U/L], while the remaining blood tests were unremarkable. A para-hilar right consolidation was seen at a chest X-ray consistent with the diagnosis of pneumonia. The patient was started on antibiotic therapy with intravenous Ceftriaxone 75 mg/Kg/day and Clarithromycin 15 mg/Kg/die. A few hours later, he developed a febrile seizure (a tonic crisis) that required three subsequent doses of benzodiazepines. Yet, post-critic hypotonia and drowsiness persisted. The cranial CT scan was negative for acute events such as bleeding, edema, or cerebral hypertension. Because of the neurological status and the underlying condition, he was transferred to our referral center. At the arrival, he was drowsy, unarousable with fixed pupil reactions bilaterally. He was in oxygen therapy in a nasal cannula with good oxygen saturation. Eupneic, a normal vesicular murmur with some bilateral crackles was appreciated. Cardiac and abdominal examinations were not significant. Given the worsening neurological conditions, the cranial CT scan was repeated but still unremarkable, while the EEG was not diagnostic. The chemical-physical analysis of Cerebral-Spinal Fluid (CSF) obtained by lumbar puncture was negative as well as cultures and the extended bacterial-viral search by polymerase chain reaction for E. coli, H. influenzae, L. monocytogenes, N. meningitidis, S. agalactiae, S. pneumoniae, Cytomegalovirus, Enterovirus, Herpes simplex 1, Herpes simplex 2, Human herpesvirus 6, Parechovirus, Varicella zoster virus, Cryptococcus neoformans/gattii. Serum B-D glucan and galactomannan were persistently negative. A chest X-ray was performed and no consolidations nor effusion or pneumothorax were found. The patient was started on broad-spectrum antibiotic therapy with meropenem, teicoplanin, ciprofloxacin, and on antimycotic therapy with fluconazole 8mg/Kg/die and acyclovir 750 mg/m2/day in three doses as antiviral and then G-CSF was added as neutrophil count dropped below 0.5 x 109/L. During hospitalization, at day +2, he had two other episodes of afebrile seizures, and an anti-edema therapy with dexamethasone was added. He underwent a naso-faringeal swab for pneumotropic agents and blood cultures. Because of the worsening of the clinical condition with a Glasgow Coma Scale of 8, at day +2 from hospitalization, he was admitted to PICU where analgesic-sedation with fentanyl and midazolam and an antiepileptic therapy with levetiracetam were started. On the same day, a cranial MRI excluded a progression of the underlying glioma (Figure 1). At days +3 and +4 the patient received a course of Intravenous Immunoglobulins as anti-inflammatory therapy (1 g/kg/day). At the nasopharyngeal swab film array, we finally found positivity for A-influenza and A-H1-influenza. In retrospect, flu-like symptoms were reported by the patient's mother and sibling. A diagnosis of Influenza Associated Encephalopathy (IAE) was made. He started

Oseltamivir therapy at 5 mg/Kg/day on day six from the hospitalization and after 9 days from the onset of fever. On day +7 a Chest X-ray showed a new left lung consolidation. The neurological status remained stable and non-reversible, he developed an increscent respiratory distress with the development of oxygen dependency, and he needed non-invasive mechanical ventilation. In three days, there was a progressive worsening that finally led to the exitus. The parents agreed with the decision to not proceed with an invasive procedure (tracheal intubation) because of the irreversibility of the neurological status and the poor prognosis. The parents refused necropsy. The events described above are listed in Table 1.

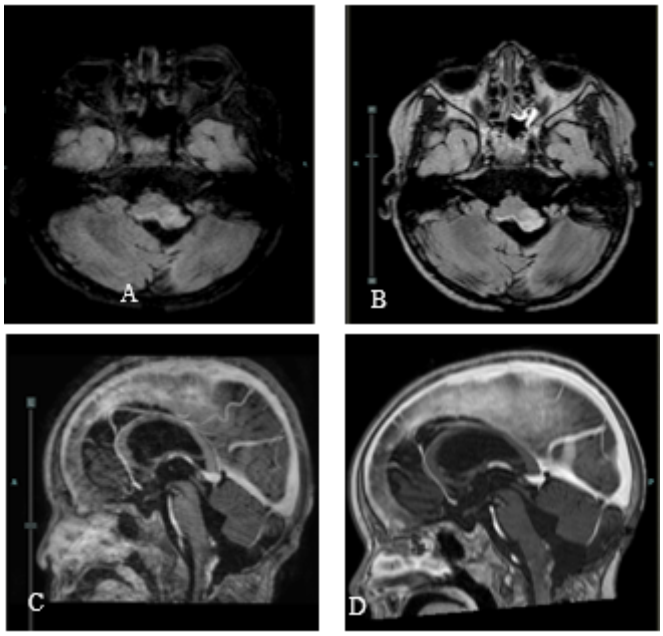

Figure 1: On the left (A-C): last follow-up MRI before the acute event (10 days before). On the right (B-D): MRI during the acute event. A-B Axial FLAIR weighted sequences. C-D Sagittal T2 weighted sequences with contrast medium. The residual cervical-medullary lesion involving the dorsal region of medulla oblongata, the cervical cord down to C3, and inferior cerebellar peduncles (> left) is remained the same comparing the last follow-up MRI and the MRI performed during the acute event. The contrast enhancement is remained the same. No evidence of new elements is shown, excluding a disease progression to explain the patient's neurological status.

	Clinical status	**Imaging/Laboratory**	**Therapy**
Day 0 Admission to a Peripheral Hospital for fever and cough	Fever and cough Onset of neurologic symptoms: 1° epileptic crisis, hypotonia and drowsiness	Routine blood tests: moderate neutropenia, CPR 27 mg/dL Chest X-Ray: Para-hilar right consolidation Encephalic CT scan negative	Start Ceftriaxone + Clarithromycin Oxygen-therapy
Day 1 Referred to Pediatric-Oncohaematology	Worsening of neurologic symptoms	2° CT scan negative Blood-cultures: negative Exams on CSF: negative EEG: diffusely hypovoltated	Started broad spectrum antibiotic therapy G-CSF

Day 2 Referred to Pediatric Intensive Care Unit	Onset of afebrile seizures Worsening of neurologic and respiratory conditions	Encephalic MRI not significant	Start Levetiracetam and Dexamethasone Analgesic-sedation Non-Invasive Ventilation
Day 3			Intravenous Immunoglobulin
Day 4 - 5			
Day 6		PCR on nasopharyngeal swab: positive for Influenza A	Start Oseltamivir
Day 7		Chest X-ray: left lung consolidation	
Days 8 - 9	Worsening clinical conditions, GCS 5-8		Supportive care
Day 10	Exitus		

Table 1: Timeline of principal events reported in the case.

Discussion

This is a case of probable Influenza-Related Encephalopathy (IAE) in an oncological patient immunocompromised by chemotherapy. There are still limited population-based studies on the clinical characteristics and burden of seasonal Influenza-associated neurological complications in the pediatric age group. The salient features of various studies conducted in the last ten years involving children with neurological manifestations of influenza are shown in Table 2.

The pathogenesis of neurologic events has not been clearly established, with both direct invasion of neural cells and inflammatory response seeming to play a role in the process [14]. The oncologic pediatric population has not been considered in any study regarding neurologic complications of influenza, but some studies demonstrated a major incidence and worse prognosis in children with generic pre-existing chronic conditions or neurological illnesses. A patient with medulloblastoma was included in a Chinese study [19]. In two Italian studies, a rate of 33% of underlying neurological conditions was found in patients hospitalized with neurological complications of influenza [13, 20]. The clinical spectrum of influenza-associated complications in children comprises different clinical entities with different prognoses. The neurological manifestation of influenza associated with the worst outcome is IAE. The mortality rate of IAE was 10.9% in a recent large retrospective study in Hong Kong [10]. Children requiring Pediatric Intensive Care Unit (PICU) admission for influenza-associated encephalopathy/encephalitis have high mortality and morbidity rates [17]; in fact, the studies conducted in the PICU setting reported also higher mortality rates: 37,5% in the study published by Lin CH et al. [19]. The hospitalized patients with influenza and neurological complications compared to other influenza in-patients without neurological manifestations had longer in-patient lengths of stays, higher rates of antiviral therapy use and mechanical ventilator use, and higher PICU admissions and influenza-related deaths [4, 15, 19]. Children <6 years old showed the highest estimated incidence of IANCs and death; in the recent retrospective study in Hong Kong, 85.5% of the IANC cases were patients aged <6 years old. This may support the fact that younger patients are more susceptible to the complications of influenza infections [10, 16]. In this case, the PCR for the influenza virus was not performed on CSF, but according to literature findings, Influenza-virus is rarely isolated from the CSF. The lack of detectable virus in CSF may be due to low viral load or the clearance of the virus from the CSF prior to sampling or may suggest that neurological manifestations are due to post-infectious inflammation rather than a direct effect of the virus. CSF cytology, protein, and glucose levels are normal in most cases, but mild pleocytosis or elevated protein levels are occasionally observed. In the case reported here, we didn't have any CT scan or MRI-positive findings. In the literature imaging positive findings are reported in a variable percentage of cases; 8% in the Chinese series [19]. Influenza should be considered in the differential diagnosis of children presenting with encephalitis and/or acute onset of neurological symptoms during the influenza season by searching respiratory viruses at least in the nasopharyngeal aspirate. Treatment is primarily supportive, and some patients may need to be referred to an intensive care unit. Antiviral therapy with a neuraminidase inhibitor is recommended especially in patients who present within 48 hours from the onset of symptoms to reduce viral replication. However, no conclusive evidence exists that oseltamivir alters the course of IAE [15, 21]. Our patient received

antiviral medication and IVIG, without any evident benefit. The efficacy of corticosteroids, IVIG, plasmapheresis, and hypothermia require further studies to be assessed. A prompt diagnosis and supportive therapy are an important burden; however, prevention is the crucial point. This case also highlights the potential role of annual influenza vaccination to prevent its complications, especially in particular populations like oncologic pediatric patients. Although influenza vaccines are strongly recommended in this group of patients, the rates of vaccination continue to be suboptimal and both parents and pediatricians fail to recognize these comorbidities as high-risk influenza conditions [13]. These findings emphasize the strategic importance of influenza immunization and highlight the need for a more active approach to vaccination in chronic patients and their family members to reduce the infectious risk.

Reference	**Type of study**	**Period of observation**	**N. of hospitalized patients with confirmed influenza**	**Number of cases with IANCs (Incidence among patients hospitalized with influenza %)**	**Mortality among those with IANCs**	**Consideration of populations with underlying conditions**	**Median age (years)**	**Flu vaccine (number of vaccinated/ total)**	**Treatment**
1 Song Y. et al. 2021 [22]	Retrospective Single-Center	2014-2019	2124	63 (2,96%) Only IAE and ANE considered	6/63 (9,5%)	no	4	0	All received Oseltamivir, Immunoglobulin, methylprednisolone
2 Mastrolia MV et al. 2019 [13]	Retrospective Single-Center	2017-2019	NA	15 (13,1%)	0%	5 (4 chronic neurological disease, 1 congenital heart disease)	2,25	0	Oseltamivir in 2 cases
3 Okuno H et al. 2018 [23]	Retrospective Multicenter	2010 - 2015	NA	IAE pediatric cases 283 2.83% (pediatrics + adults)	22/283 7,8%	no	7 (in this study there were also adults)	N/A	N/A
4 Antoon JW et al. 2021 [6]	Multi-center cross-sectional	2015 - 2020	29.676	2246 (7.6%) 4% excluding febrile seizures	63 (2,8%)	Chronic neurologic conditions 8,1%	NA	N/A	Oseltamivir
5 Cleuziou P et al. 2021 [17]	Retrospective Multicenter Study (PICU)	2010 - 2018	NA	41	7 (17%) PICU	Exclusion criteria: preexisting chronic neurologic disorder	4,7	N/A	49% steroids

6 Frankl S et al. 2021 [15]	Retrospective Single-Center	2010 - 2017	1217	131 10,8%	0	Pre-existing neurologic diagnosis 74/131 (56%)	5,6	57/131 (44%)	Oseltamivir 86% Steroids 29%
7 Lin CH t al. 2021 [19]	Retrospective Single-Center (PICU)	2012 -2019	1532	16 1% (only patients admitted to PICU were considered)	6/16 (37,5%) (only patients admitted to PICU were considered)	4 underlying disorder: 3 neurodevelopmental disorders 1 medulloblastoma	5,3	N/A (none of the 6 patients who died)	All Oseltamivir
8 Solis-Garcia G et al. 2020 [11]	Retrospective Single-Center	2015 - 2018	245	29 (11,8%)	0	Previous underlying condition 47,8% (of all 245 patients)	1,75 (all 245 patients)	N/A	86% Oseltamivir
9 Britton PN, Dale RC et al. 2017 [4]	Retrospective Multi-Center	2013 - 2015	NA	13	2/13 (15,4%)	Past history of neurological disease 2/13 (15,4%)	3,7	0	2/13 oseltamivir 8/13 (62%) corticosteroids
10 Rao S et al. 2020 [13]	Retrospective Multi-Center	2016 - 2017	182	33/182 (18%)	0	Underlying neurological condition 10/33 (30%)	6	14/33 (42,2%)	32 (97%) Oseltamivir
11 Takia L et al. 2020 [24]	Retrospective single-center	2019	68 (only A-influenza)	6/68 (8,8%)	1/6	0/6	2,1	N/A	All Oseltamivir 3/6 methylprednisolone
12 Muhammad Ismail HI et al. 2014 [25]	Retrospective Multicenter	2009	1244 (Only A H1N1)	103/1244 (8,3%)	4/103	28% pre-existing neurological illness	4,2 years	N/A	N/A
13 Kawashima H et al. 2012 [26]	Retrospective Multicenter	2009 - 2010	N/A	207 (188 enrolled in the study for outcome)	16/188 (8,5%)	N/A	N/A	77/188	180/188 Oseltamivir

14 Britton PN, Blyth CC et al. 2017 [7]	Retrospective Multicenter	2013 - 2015	710	54 (7,6%)	3/54 (6%)	Pre-existing neurological disease 17/54 (35%)	3,8	2/54 (4%)	Oseltamivir 8/47 (17%)
15 Paksu MS et al. 2017 [16]	Retrospective Multicenter	2015 - 2016	NA	14 (Only severe neurological complications considered)	1/14 (7,1%)	4/14 (28,6%) comorbidities	4,9	0/14	Oseltamivir 13/14 Iv Ig 6/14 Corticosteroid 1/14
16 Yu MKL et al. 2022 [12]	Retrospective Multicenter	2014 - 2018	28.016	2483 (8,9%)	7 (0,28%)	61 (2.46%) Pre-existing neurological disorder	3 years	N/A	Antiviral 917 (36.9%)
17 Chen LW et al. 2018 [27]	Retrospective Multicenter	2014 - 2017	N/A	10	0	4/10 past medical history	5,9	4/9 (1 unknown)	10/10 antiviral
18 Choi GJ et al. 2021 [28]	Retrospective Multicenter	2010 - 2017	1988	161 (8,1%)	2 0,62%	24 (15%) Underlying neurological disease	NA	N/A	N/A
19 Okumura A et al. 2012 [29]	Retrospective multicentric	2009	NA	20 (Only A H1N1 severe IAE)	16/20 (20%) (Only severe cases of IAE)	5/10 (25%) Pre-existing condition	3,75 years	N/A	Antiviral 10/20
20 Wilking AN et al. 2014 [30]	Retrospective Monocenter	2009 - 2010	365 (only influenza A H1N1)	32/365 (8,8%)	0	12/32 (37%) Pre-existing nditions	4	N/A	31/32 Oseltamivir 1/32 corticosteroids
21 Goenka A et al. 2014 [31]	Retrospective Multicenter	2011 - 2013	NA	21 children 4 adults (tot 25)	4/25 (comprehensive of adult cases) 16%	6/21 preexisting neorological disorders	4	0	Oseltamivir 23/25

22 Khandaker G et al. 2012 [32]	Retrospective Multicenter	2009	506 (only A-H1N1)	49 (9,7%)	2/49 4,1%	55.1% had preexisting medical conditions 42.8% had preexisting neurologic conditions	3,7	7/49 (14,3%)	N/A

Table 2: The salient features of various studies conducted in the last ten years involving children with neurological manifestations of influenza. IANCs: Influenza Associated Neurological Complications. IAE: Influenza-Associated Encephalitis. ANE: Acute Necrotizing Encephalopathy. PICU: Pediatric Intensive Care Unit. N/A: Not Available

Declarations

Consent for publication

Informed consent was obtained from the parents for publication.

Competing interests

All authors have no competing interests to declare pertaining to this manuscript.

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