**ARC Journal of Pediatrics**
*Volume 9 Issue 2, 2024, PP 7-11*
*ISSN No. (Online) 2455-5711*
*DOI: https://doi.org/10.20431/2455-5711.0902002*
*www.arcjournals.org*

# Neurological Involvement in Children with Influenza A (H1N1): A Case Series from a Second-Level Hospital in Italy

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## Abstract

**Background:** *Influenza is one of the most common causes of acute respiratory tract infection in children during winter season. Although usually self-limiting, it may lead to neurological complications which, in severe cases, can be fatal. This study aims to determine the extent and severity of neurological complications due to Influenza A (H1N1) in children during the 2023-2024 flu season.*

**Methods:** *We retrospectively enrolled all children admitted to our second-level hospital between September 2023 and March 2024 with a microbiologically-confirmed H1N1 Influenza infection and neurological manifestations. Demographic, clinical, laboratory, instrumental, management and outcomes data were evaluated by analyzing the electronic medical charts.*

**Results:** *Out of 252 nasopharyngeal swabs sent to the microbiological laboratory, 29 cases (12%) were positive for H1N1 Influenza. Five patients were excluded and 7 out of 24 children (29%) developed concomitant neurological involvement so they were included in our series. The most frequent neurologic symptoms were seizures (6/7, 86%); two of these patients developed status epilepticus and in one case seizures were associated to confusion, hallucinations, and movement disorder. One patient exhibited irritability and lethargy (1/7, 14%). Three patients (43%) received antiviral treatment (Oseltamivir). Two patients (29%) were admitted to a pediatric intensive care unit. Six patients (86%) fully recovered without sequelae, while one experienced permanent neurological impairment.*

**Conclusions:** *Neurological manifestations related to Influenza are usually self-limiting, but in some cases, they may require hospitalization and can lead to severe outcomes or even permanent disability. Therefore, influenza vaccination should be highly recommended in the pediatric population.*

**Keywords:** *Influenza A, H1N1, children, neurological involvement, seizures.*

## 1. Introduction

Influenza is a leading cause of morbidity in children during winter. Its typical symptoms include fever, headache, cough, sore throat, myalgia, and sometimes diarrhea and vomiting. While usually self-limiting, children, elderly people, immuno compromised individuals, and pregnant women face a higher risk of complications. [1]

Influenza is associated to a high risk of neurological complications, ranging from 8 to 30% in pediatric cases. [2–5] These manifestations vary from minor changes in mental state, dizziness, and simple febrile seizures to severe complications like status epilepticus, influenza-associated encephalitis/ encephalopathy (IAE), meningitis, stroke, Reye syndrome and demyelinating disorders.[1,6] Even though neurological manifestations often resolve on their own, severe cases may lead to permanent sequelae or death.[1,6]

The H1N1 subtype is transmitted via airborne droplets and typically causes flu-like symptoms. Though most cases are mild, several studies have highlighted the severity of influenza A infection in children. [6–8] However, studies on neurological manifestations of H1N1 in pediatric patients are limited. Additionally, comprehensive epidemiologic data on this issue are lacking.[6] This study aims to analyze the clinical variability, severity, and outcomes of pediatric H1N1 infections with neurological involvement.

## 2. Materials and Methods

This retrospective study includes all children diagnosed with Influenza A (H1N1) and neurological symptoms from September 2023 to March 2024 in our second-level hospital in Italy. Patients were enrolled by searching the nasopharyngeal (NF) swabs database of our reference microbiological laboratory.

Demographic, clinical, laboratory, management and outcomes data were obtained from the electronic medical records. Inclusion criteria were pediatric patients aged 30 days-16 years, confirmed H1N1 positivity through polymerase chain reaction (PCR) testing on NF swabs (sent from the pediatric Emergency Department (ED) or from the pediatric ward), and neurological symptoms at any time of the illness course. Patients without sufficient clinical data were excluded. Informed consent was obtained from all subjects involved in the study.

## 3. Results

Out of 252 NF swabs, collected in the pediatric department of our hospital, 29 (11.5%) tested positive for H1N1. Four patients were excluded due to missing clinical and one because of age under 30 days. Of these 24 children, seven (29.2%) met the inclusion criteria, showing neurological involvement. The other symptoms included respiratory tract manifestations (12/24, 50%), reduced feeding (3/24, 12.5%), myalgia/myositis (2/24, 8.3%), skin rash (1/24, 4.2%) and gastroenteritis (1/24, 4.2%).

As summarized in Table 1, among the seven cases, six (85.7%) were male, with a median age of 36 months (interquartile range [IQR]: 13.5-45).

**Table 1.** *Demographic, clinical, management and outcome data of the seven children with Influenza A H1N1 and neurological involvement.*

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| **Gender** | M | M | M | M | M | M | F |
| **Age (months)** | 2 | 36 | 11 | 16 | 133 | 38 | 52 |
| **Ethnicity** | Caucasian | Caucasian | Caucasian | North African | Asiatic | Caucasian | Caucasian |
| **Underlying conditions** | - | - | - | - | Mental retardation | - | Behavioural disorder, language delay |
| **Anti-Influenza vaccination** | No | No | No | No | No | No | No |
| **Clinical symptoms (other than neurologic)** | Fever, reduced feeding | Fever | Fever | Fever | Fever, cold | Fever | Fever, cough |
| **Neurologic symptoms** | Irritability and lethargy | Complex FS (repetitive episodes) | Status epilepticus | Status epilepticus | Seizures, confusion, hallucinations, walking instability, Romberg + | Complex FS (repetitive and focal) | Simple FS |
| **Time between illness onset and neurologic symptoms (days)** | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| **CRP value at admission (mg/dL)** | 1.66 | 5.2 | 0.63 | 0.14 | 2.39 | 1.65 | 1.62 |
| **Viruses on NF swabs** | Low viral load H1N1 | High viral load H1N1 | High viral load H1N1 | Intermediate viral load H1N1 | Intermediate viral load H1N1 | not known viral load H1N1 | Intermediate viral load H1N1, Adenovirus and RSV |
| **Instrumental investigations** | | | | | | | |
| **EEG** | NP | Generalized slowing | Generalized slowing | Normal* | NP | Normal | NP |
| **Cranial CT** | NP | NP | Normal | Normal | NP | NP | NP |
| **Brain MRI** | NP | NP | Cortical alterations and ventricles dilation | Normal | NP | NP | NP |
| **Others** | TF US (normal) | - | - | - | - | - | - |
| **CSF analyses** | Negative | NP | Negative | Negative | NP | NP | NP |
| **Treatments** | | | | | | | |
| **Anti-epileptic drugs** | - | - | er diazepam, iv midazolam | er diazepam, iv midazolam, iv phenytoin | - | - | - |
| **Anti-viral drugs** | Oseltamivir | - | Oseltamivir | Oseltamivir | - | - | - |
| **Ward admission** | Yes | Yes | Yes | Yes | Yes | Yes | No |
| **PICU admission** | No | No | Yes | Yes | No | No | No |
| **LOS (days)** | 6 | 5 | 58 | 6 | 4 | 4 | 2 |
| **Outcome** | No sequelae | No sequelae | Neurovege-tative state | No sequelae | No sequelae | No sequelae | No sequelae |

** The EEG was performed a few days after the onset of clinical symptoms in a neurologically healthy patient.*

*CRP: C-reactive protein; CSF: cerebrospinal fluid; CT: computed tomography; EEG: Electroencephalogram; FS: febrile seizures; ER: endorectal; IV: intravenous; LOS: length of hospital stay; MRI: magnetic resonance imaging; NF: nasopharyngeal; NP: not performed; PICU: pediatric intensive care unit; RSV: respiratory syncytial virus; TF: transfontanellar; US: ultrasound.*

Five out of seven children (71.4%) were previously healthy. Patient 5 had mental retardation, with ongoing genetic investigations due to parental consanguinity, while patient 7 had a behavioral disorder and language delay. None of the children received a seasonal influenza vaccination.

All cases presented with fever (temperature >37.5°C). Other symptoms are outlined in Table 1.

The median time between illness onset and neurological symptoms was 0.6 days (range 0-1).

Six children (85.7%) experienced seizures; one (14.3%) had simple febrile seizures (FS) and two (28.6%) had complex FS. Patient 3 and 4 (28.6%) developed status epilepticus. Patient 5 exhibited seizures, transient confusion, hallucinations, walking instability, and a positive Romberg sign. An infant (patient 1) developed irritability and lethargy.

Blood tests were performed at admission, and almost all cases showed a mild increase in C-reactive protein (Table 1) with a median of 1.64 (IQR 1.13-2.03) mg/dL. Liver and kidney function tests were normal for all patients at admission.

All NF swabs tested positive for H1N1 with varying viral loads and one child also had co-infections with other viruses (Table 1).

Electroencephalogram (EEG) was performed in four children (57.1%), showing generalized slowing of background activity compatible with encephalopathy in two cases.

Two patients (28.6%) underwent brain imaging due to severe disease course with persistent consciousness alterations. Computed tomography (CT) resulted negative, while magnetic resonance imaging (MRI) revealed diffuse cortical signal alterations and dilatation of the cerebral ventricles in patient 3.

Lumbar puncture was performed in three children (42.9%). The physical-chemical examination, microbiological panel and culture of the cerebrospinal fluid (CSF) were negative in all cases, including for H1N1 as confirmed by PCR testing.

Regarding treatment, 3 patients (42.9%) received antiviral therapy with Oseltamivir and two also required antiepileptic treatment.

Six children (85.7%) were admitted to the pediatric department for further observation, with a median length of stay of 4.2 days (range 2-6). The two cases with status epilepticus did not respond to antiepileptic treatment; one of them even developed respiratory failure requiring ventilatory support, and both were transferred to the nearest tertiary care pediatric hospital and admitted to pediatric intensive care unit (PICU). Patient 3 later developed also severe hepatic and renal failure and was subsequently diagnosed with Febrile Infection-Related Epilepsy Syndrome (FIRES).

This child still presents with permanent neurovegetative outcomes, while the other patients (6/7, 85.7%) fully recovered without sequelae.

## 4. Discussion

This study investigates the clinical profile and outcomes of pediatric patients with Influenza A (H1N1) infection and associated neurological symptoms. Our findings highlight the complex interaction between respiratory infection and neurological manifestations, underlining the importance of vigilant monitoring in pediatric populations.

In our cohort of 24 children with microbiologically confirmed H1N1 infection, 29% of them exhibited neurological symptoms. This frequency aligns with existing literature, where neurological complications are reported in up to 8-30% of pediatric patients; that indicates that neurological involvement can often arise from viral infections, including influenza, and highlights the need for healthcare providers to be aware of these potential complications.[2–4]

As already specified by other papers, we suggest that all children who are admitted with neurological findings, especially during the influenza season, should be evaluated for influenza-related neurological complications even if their respiratory complaints are mild or nonexistent.[3,9]

Pre-existing neurological or neuromuscular diseases are reported risk factors for influenza-related neurologic complications.2,3 Notably, most of our patients were previously healthy, emphasizing that even children without

underlying conditions can experience severe complications. [3]

The diversity of neurological manifestations observed—ranging from simple FS to more severe conditions such as status epilepticus and IAE—reflects the spectrum of possible complications following H1N1 infection. [6, 9–11]

The occurrence of seizures in 86% of our patients is particularly noteworthy and both simple and complex febrile seizures were documented, as well as status epilepticus. These findings are consistent with previous studies.[2,8] Influenza is linked to an increased risk of seizures, possibly due to fever and direct viral effects on the central nervous system.8

Our experience showing that six out of seven patients fully recovered without sequelae is encouraging. However, encephalopathy and FIRES represent severe illness course that can result from viral infections, highlighting the potential for significant morbidity.3 The persistence of neurological deficits in one of our patients stresses the need for prompt diagnosis and management of severe neurological complications.

The diagnostic workup revealed H1N1 by PCR in all NF swabs, with one case of coinfection. This highlights the importance of comprehensive viral testing in cases of suspected viral neurological involvement. The negative CSF findings in our cohort, including PCR for influenza virus genome, suggest that direct viral invasion do not occur in all cases, as confirmed by other studies.1–3 Additionally, the inflammatory response elicited by H1N1 may still contribute to neurological symptoms.[12]

Moreover, the utilization of neuroimaging such as MRI and cranial CT were not definitive in all cases, but they may provide valuable insights and can be crucial in assessing severe neurological involvement.[13]

Treatment strategies varied, with 43% of patients receiving antiviral therapy with Oseltamivir.

While the clinical efficacy of antivirals in severe H1N1 cases remains debated, their use in our cohort may have contributed to the positive outcomes observed in the majority of patients.[14]

Previous studies suggest that early antiviral treatment can reduce the duration of symptoms and complications associated with H1N1.[15,16]

Additionally, the management of seizures with antiepileptic drugs demonstrates the need for rapid intervention in neurologically compromised children.

Most of our patients have been hospitalized and 2/7 required admission to PICU, with a longer length of hospital stay. This finding underlines the need for specialized care in severe cases and highlights the resource implications for healthcare systems dealing with such complications.[7]

The fact that our patients did not receive seasonal influenza vaccination reinforces the need to improve vaccination campaigns and other public health strategies to protect vulnerable populations, including the pediatric one. Specifically, Influenza vaccination is mostly recommended in Italy in children aged 6 months to 6 years; in accordance, this age group is the one considered at higher risk of neurologic complications in the literature and in our series most children were about 1 to 4 years old.[2,5]

## 5. Conclusion

This study reinforces the need for awareness of potential neurological complications in pediatric patients with Influenza A (H1N1) infection. Early recognition and intervention are crucial in managing these patients to optimize outcomes. Therefore, all children presenting with neurological symptoms during the Influenza season, should be screened for Influenza infection, especially since an effective treatment is available.

Future studies should aim to establish clearer links between H1N1 and neurological outcomes, including larger cohort analyses and longitudinal studies to track the long-term effects of H1N1-related neurological complications in children.

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**Citation:** *Serena Chiellino et al. Neurological Involvement in Children with Influenza A (H1N1): A Case Series from a Second-Level Hospital in Italy. ARC Journal of Pediatrics. 2024; 9(2):7-11. DOI: https://doi.org/10.20431/2455-5711.0902002.*