

## Pediatric Neuroinvasive West Nile Virus Disease during the 2024 Outbreak in Annaba, Algeria

DJ. Belamri<sup>(1)</sup>, A. Bentorki<sup>(2)</sup>, H. Sehab,<sup>(3)</sup> A. Bouguizi<sup>(4)</sup>, S. Nadjai,<sup>(5)</sup> A. Bouaricha<sup>(6)</sup>

<sup>1,3,5</sup>Professor, <sup>2,4,6</sup>Assistant Professor,

<sup>2</sup>Department of Pediatric Intensive Care Unit,

<sup>3</sup>Department of Pediatrics, <sup>4</sup>Department of Epidemiology,

<sup>5,6</sup>Department of Bacteriology and Virology,

Sainte Thérèse Clinic, University Hospital of Annaba.

University Hospital of Annaba

**\*Corresponding Author:**

**Amina Bougouzi**

Assistant Professor, Department of Epidemiology, University Hospital of Annaba

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

### Abstract

**Keywords:** NIL

### Introduction

West Nile virus (WNV) is an arbovirus transmitted to humans through the bite of infected ornithophilic mosquitoes, most commonly *Culex* species, after feeding on viremic migratory birds that act as reservoirs and amplifying hosts [1]. In contrast, human viremia is short-lived and of low titer, insufficient to infect mosquitoes, making humans accidental hosts [2]. WNV is maintained in nature through a mosquito–bird enzootic cycle.

Since the late 1990s, WNV has emerged as a major public health concern due to recurrent outbreaks, its rapid geographic expansion, and the occurrence of severe neuroinvasive disease [1]. First isolated in Uganda in 1937, WNV caused only sporadic epidemics with rare neurological involvement until the 1990s [3]. Subsequently, significant outbreaks were reported in Algeria (Timimoun, 1994: 50 cases including 8 deaths) [4], Romania in 1996, Tunisia in 1997, and Russia in 1999 [5]. Today, WNV is present on all continents, with the United States remaining the most important epidemic focus since 1999.

Clinically, WNV infection is asymptomatic in more than 80% of cases. Approximately 20% of patients, including children, develop an influenza-like illness,

while fewer than 1% present with neuroinvasive disease such as meningitis, encephalitis, meningoencephalitis, or acute flaccid paralysis [6]. Diagnosing these forms is challenging in developing countries, including Algeria, where most causes of encephalitis remain unexplained and where cross-reactivity with other flaviviruses complicates laboratory confirmation [6].

The natural history and clinical spectrum of WNV infection in the pediatric population remain poorly defined, mainly due to underdiagnosis. Most available epidemiological and clinical data originate from the United States, which has experienced recurrent epidemics since 1999. Between 1999 and 2016, the CDC recorded 2,397 pediatric cases (<19 years), of which 34% had neuroinvasive disease [7]. In Europe, available data are limited to small case series.

In Algeria, WNV was first isolated in 1968 from *Culex* mosquitoes in Djanet. More recently, an outbreak occurred in Batna and Msila in 2023, resulting in 53 confirmed cases including 10 deaths [8]. In August 2024, Annaba, located in northeastern Algeria, experienced its first epidemic of severe neurological forms of WNV. This region is a marshy area situated

along a major bird migration corridor and is characterized by abundant mosquito populations and favorable climatic conditions (heat and humidity), all of which contribute to the risk of WNV circulation. During this outbreak, 14 children with severe neuroinvasive forms were hospitalized at the Sainte-Thérèse Pediatric Clinic of Annaba University Hospital.

The objective of this study was to describe the epidemiological, clinical, paraclinical, and short- to medium-term outcomes of pediatric neuroinvasive WNV infection observed during the 2024 outbreak in Annaba.

## Patients And Methods

### Study Design And Setting.

We conducted a prospective, descriptive study during the West Nile virus (WNV) outbreak that occurred between August 2 and October 30, 2024, at the Sainte-Thérèse Pediatric Clinic, Annaba University Hospital. Patients were hospitalized either in the general pediatrics ward or in the pediatric intensive care unit.

### Participants :

The study included 14 consecutive children (9 males, 5 females) admitted with suspected neuroinvasive WNV infection.

### Case Definitions :

Meningitis: cerebrospinal fluid (CSF) pleocytosis and/or elevated protein associated with compatible meningeal signs.

Encephalitis: altered mental status lasting  $\geq 24$  hours and/or seizures, with or without focal neurological signs; electroencephalogram (EEG) or neuroimaging findings were considered when available.

Meningoencephalitis: concurrent features of meningitis and encephalitis, often preceded by a prodromal syndrome (fever, headache, myalgia, rash).

Acute flaccid paralysis (AFP): sudden onset of flaccid weakness with reduced or absent deep tendon reflexes.

### Data Collection :

Epidemiological data (exposure, residence, travel history), clinical characteristics (symptoms, neurological signs, Glasgow Coma Scale), laboratory parameters, EEG, neuroimaging, treatments, and

outcomes (in-hospital and follow-up) were recorded using a standardized case-report form.

### Laboratory Investigations :

Serological diagnosis of WNV was performed at the Arboviruses and Emerging Viruses Laboratory of the Institut Pasteur of Algeria, using ELISA for detection of anti-WNV IgM and IgG in serum, and IgM in CSF. To rule out cross-reactivity, selected sera were tested against antigens from other arboviruses. Molecular detection of WNV RNA by RT-PCR was performed on CSF, serum, and urine samples, but all tests were negative. Sample collection, packaging, and transport followed the procedures outlined in Ministerial Note No. 9 (June 9, 2024) on the reactivation of the national West Nile fever surveillance and alert system.

### Outcomes :

The primary outcome was the characterization of the different neuroinvasive clinical forms of WNV and their in-hospital evolution. Secondary outcomes included the short-term status at discharge and the medium-term prognosis during outpatient follow-up. Quantitative variables were summarized as means  $\pm$  standard deviation (SD) or medians with interquartile ranges (IQR), depending on their distribution. Categorical variables were expressed as frequencies and percentages. Comparative analyses were performed using the Chi-square test or Fisher's exact test for categorical variables, and the Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Statistical significance was defined as a p-value  $< 0.05$ . Data entry and statistical analyses were performed using Epi Info version 2000.

### Ethics :

The study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the institutional ethics committee (insert name/approval number). Written informed consent was obtained from the parents or legal guardians of all participants, with assent from older children when appropriate.

### Results :

#### Epidemiological Characteristics :

During the study period (August–October 2024), 14 pediatric cases of neuroinvasive West Nile virus (WNV) infection were hospitalized. The mean age was 9.8 years (range: 3–16), with a male

predominance (9 boys, 5 girls). The highest incidence was observed in September, which coincided with increased rainfall and higher ambient temperatures. All patients resided in peri-urban areas of Annaba.

### **Clinical Presentation :**

Fever and headache were reported in all patients (100%). Signs of meningeal irritation were present in 10 children (71.4%). Neurological manifestations included altered consciousness in 9 patients (64.3%), seizures in 5 (35.7%), psychiatric disorders in 4 (28.6%), and tremors in 2 (14.3%). Acute flaccid paralysis (AFP) was documented in 2 patients, one of whom also presented with encephalitis. These patients exhibited areflexia, sensory deficits, and multiple cranial nerve impairments (aphasia, dysarthria, dysphonia, swallowing difficulties).

### **Paraclinical Findings :**

Lumbar puncture revealed cytochemical abnormalities in 12 patients (85.7%), with lymphocytic pleocytosis and moderate hyperproteinorachia. Magnetic resonance imaging (MRI) performed in 4 children demonstrated abnormalities in 2 cases, including meningeal enhancement and hyperintense lesions in cortical and subcortical regions. Electroencephalography showed diffuse slowing in 3 patients. Electromyography in one AFP case confirmed axonal motor neuropathy.

### **Biological Confirmation :**

Serological testing performed at the Institut Pasteur of Algiers detected WNV-specific IgM antibodies in serum and/or cerebrospinal fluid in all patients. IgG seroconversion was observed in 10 cases (71.4%). Cross-reactivity with other arboviruses was excluded through complementary serological testing. Viral RNA was not detected by RT-PCR in any of the samples.

### **Complications And Outcomes :**

Eight patients (57.1%) required admission to the pediatric intensive care unit for neurological or respiratory complications. Four children developed severe encephalitis with rapid deterioration of consciousness and autonomic dysfunction. The case fatality rate reached 76% (11/14), with deaths occurring primarily among patients presenting with encephalitis and AFP. Surviving patients (3/14, 21.4%) exhibited persistent neurological sequelae at

hospital discharge, including motor deficits and speech impairment.

### **Statistical Analysis :**

Comparisons between patients with meningoencephalitis and those with meningitis alone showed no significant differences in age ( $p=0.41$ ) or sex distribution ( $p=0.417$ ). The presence of encephalitis was strongly associated with adverse outcomes, although no additional statistical associations reached significance.

### **Discussion :**

In this study, more than half of the patients developed symptoms in September, coinciding with high rainfall and elevated temperatures. These climatic conditions, characteristic of the late summer period of 2024 (August–October), were favorable to the proliferation of *Culex* mosquitoes, the main vectors of WNV (Fig. 1). This temporal distribution is consistent with previous findings reporting that human WNV infections in temperate regions typically peak in late summer and early autumn [11]. While cases are increasingly reported throughout the year in certain settings [8], epidemics remain recurrent in the Maghreb and other regions with similar climates, often linked to urban mosquito proliferation.

Transmission of WNV to humans is primarily vector-borne, occurring through the bite of an infected ornithophilic mosquito. Other transmission routes, such as blood transfusion, organ transplantation, vertical transmission, breastfeeding, and occupational exposure, have been described [12–14]. However, given the negative results of epidemiological investigations in our patients, vector transmission remains the most plausible mode in this outbreak.

The clinical spectrum of WNV infection in children is poorly documented, largely due to underdiagnosis and the scarcity of published pediatric series. Data from the United States suggest that most pediatric infections are asymptomatic ( $\approx 80\%$ ) or present as a non-specific febrile illness ( $\approx 20\%$ ) [7]. In our series, almost all children presented with fever, severe headaches, myalgia, pharyngitis, asthenia, and gastrointestinal symptoms within the week preceding hospitalization (Fig. 2), consistent with known prodromal features.

Severe neuroinvasive forms remain rare ( $<1\%$  of cases), but they were strikingly predominant in our

cohort. In the United States, pediatric neurological involvement accounts for  $\approx 4\%$  of reported cases, with an estimated annual incidence of 0.68 per million children [8]. The neurological manifestations we observed—meningitis, encephalitis, meningoencephalitis, acute flaccid paralysis (AFP), seizures, and extrapyramidal signs—overlap with those described in the literature [5,15–17]. Notably, seizures with rapid deterioration of consciousness were almost universal, leading to early admission to intensive care. Two patients developed AFP, one with quadriplegia and one with paraplegia, further illustrating the spectrum of WNV neurological involvement.

The severity of our cases was remarkable. Twelve patients experienced life-threatening complications, and the mortality rate reached 76%, which far exceeds the  $\approx 10\%$  mortality reported in the literature for neuroinvasive forms [20]. Several factors may account for this unusually high fatality rate: the naïve status of the exposed pediatric population, the abrupt clinical progression, delays in referral, and possibly the virulence of the circulating viral strain. In contrast with adults, in whom advanced age, chronic comorbidities, and immunosuppression are recognized risk factors [12], none of our patients had predisposing conditions, reinforcing the hypothesis that the emergence of WNV in an immunologically naïve population contributed to the exceptional severity of this outbreak.

Ophthalmological involvement, although rarely reported in children, was observed in one patient who presented with retinal hemorrhage and chorioretinal scars. This finding is in line with previous studies describing ocular manifestations, including chorioretinitis, retinal vasculitis, and optic neuritis [12].

Neuroimaging findings were nonspecific in most patients, with either normal results or signs compatible with encephalitis/meningoencephalitis. Although T2 hyperintensities in the thalamus, basal ganglia, or brainstem have been suggested as early indicators of WNV encephalitis [5], these were not consistently observed. Electromyography, performed in one patient with AFP, revealed features consistent with motor axonal polyneuropathy, in agreement with published descriptions [17].

From a diagnostic perspective, confirmation of WNV infection relies on the detection of specific IgM antibodies in serum or CSF, or on viral RNA detection by RT-PCR [3,18]. In our cohort, CSF IgM positivity was documented in two patients, while the diagnosis in others relied on epidemiological context and compatible neurological symptoms. The failure of viral isolation in CSF samples was most likely due to low viral load and suboptimal storage conditions during transfer. Unfortunately, confirmatory late serological testing was not possible in several cases due to rapid fatal outcomes.

Currently, no specific antiviral treatment exists for WNV infection. Management is symptomatic, including supportive care, fluid resuscitation, antipyretics, corticosteroids, antibiotics, and in some cases immunoglobulins [19]. Despite these interventions, the high lethality observed in our series underscores the urgent need for preventive strategies, including vector control and public health awareness during epidemic periods.

The medium-term outcome of survivors was heterogeneous. Three patients improved but retained sequelae such as seizures, persistent headaches, monoparesis, tremors, concentration difficulties, and visual disturbances. One patient deteriorated after discharge, developing recurrent seizures that progressed to fatal status epilepticus. These outcomes mirror those reported in adults, where persistent neurological and cognitive impairments are not uncommon [5].

Overall, this series highlights the unexpectedly severe clinical presentation and high mortality of pediatric WNV infection in Annaba in 2024. These findings emphasize the need for heightened clinical suspicion, rapid referral, and strengthened epidemiological surveillance to prevent and mitigate future outbreaks.

## Conclusion

West Nile virus (WNV) is responsible for a growing number of neuroinvasive infections worldwide. Our study demonstrates that pediatric neurological forms are more frequent and severe than commonly reported, with life-threatening outcomes in most cases. These findings emphasize the urgent need for strengthened epidemiological surveillance, effective vector control strategies, and a high index of clinical suspicion for

WNV in children residing in or returning from endemic areas during the transmission season.

Conflict of interest: The authors declare no conflict of interest.

## References

1. Rizzoli A, Jimenez-Clavero MA, Barzon L, et al. Le défi du WNV en Europe : lacunes dans les connaissances et priorités de recherche. *Euro Surveill.* 2015 ;20 (20) :pii :21135 .
2. Hayes EB, Gubler DJ. WNV : épidémiologie et caractéristiques cliniques d'une épidémie émergente aux USA. *Ann Rev Med* 2006 ;57 :181e94.
3. Mandji Lawson JM, Mounguengui D, et al. Un cas de méningoencéphalite à virus West Nile à Libreville Gabon. *Med Trop* 2009;69 :501-502.
4. Benjelloun A, El Harrak M, Belkadi B. West Nile Disease Epidemiology in North-West Africa : Bibliographical Review, *Transboud. Emerg.Dis.* (2016)
5. Hachfi. W, Bougmiza. I, Bellazreg. F, et al. Une 2ème épidémie de méningo-encéphalite à virus West Nile en Tunisie. *Med et Maladies Infectieuses* 40 (2010) 456-61.
6. Smith. JC, Mailman. T, Mac Donald. NE. Virus du Nile occidental : Les pédiatres devraient-ils d'en soucier ? *Journal of infection* (2014), <http://dx.doi.org/10.1016/j.inf.201407.019>.
7. Savasta.S, Rovida. F, Foadelli. T, et al. Encéphalite à virus West Nile chez un cas pédiatrique immunocompétent. *Italian J of Pediatr* (2018) 44 : 140 <http://doi.org/10.1186/s13052-018-0574-x>
8. Centres pour le contrôle et la prévention des maladies. WNV occidental-Cartes et données cumulatives finales pour 1999-2016. <https://www.cdc.gov/westnile/statsmaps/CumMapsData.html>.
9. Lafri I, Prat CM, Bitam I, Gravier P, et al. Seroprevalence of WNV antibodies in equids in the North-Est of Algeria and detection of virus circulation in 2014, *Comp. Immuno. Microbiol. Infect. Dis* (2017).
10. Décret exécutif n° 22-250 du Aouel Dhou El-Hidja 1443, correspondant au 30 Juin 2022 fixant la liste des Maladies Transmissibles soumises à Déclaration Obligatoire (MDO).
11. Campbell GL, Marfin AA, Lanciotti RS, et al. WNV. *Lancet Infect Dis* 2002 ;2 :519-29.
12. Guyon G, Ladet S, Maestracci, et al. Infections WNV en Pédiatrie. *Arch Pediatr* 2009;16 :S85-S88.
13. O'Leary DR, Kuhn S, Kniss KL, et al. Birth outcome following Wnv infection of pregnant women in USA : 2003-4 *Pediatrics* 2006 ;117 :537-45.
14. Hinckley AF, O'Leary DR, Hayes ES. Transmission of WNV through human breast milk seems to be rare. *Pediatrics* 2007 ;119 :666-73
15. Solomon T, Flavivirus encephalitis. *N Eng J Med* 2004 ;351 :351-8
16. Kramer LD, Li J, Shi PY. West Nile Virus. *Lancet neurol* 2007 ;6 :171-81.
17. Clé M, Eldin P, Briant L, et al. Impacts neurocognitifs des infections à arbovirus. *Journal of Neuroinflammation* (2020) 17 :233. <https://doi.org/10.1186/s12974-020-01904-3>
18. Andrew Yu, Emily Ferenczi. MD, Kareem M, et al. Spectre clinique du WNV occidental : Maladie neuroinvasive. *Sagepub.com/journals-permissions* doi :10.1177/194187441 9868636 *Journals.sagepub.com* (2019) /home/NHO.
19. Ben-Nathan D, Gershoni-Yahalom O, Samina I, et al. Utilisation d'immunoglobulines intraveineuses à titre élevé contre le WNV occidental provenant de donneurs israéliens sélectionnés pour le traitement de l'infection par le WNV. *BMC Infect Dis* 2009 ;9 :18. <http://dx.doi.org/10.1186/1471-2334-9-18>
20. Nash D, Mostashari F, Fine A, et al. The outbreak of WNV infection in the New York City area in 1999. *N.Engl J. Med* 2001 ;344 :1807-14.

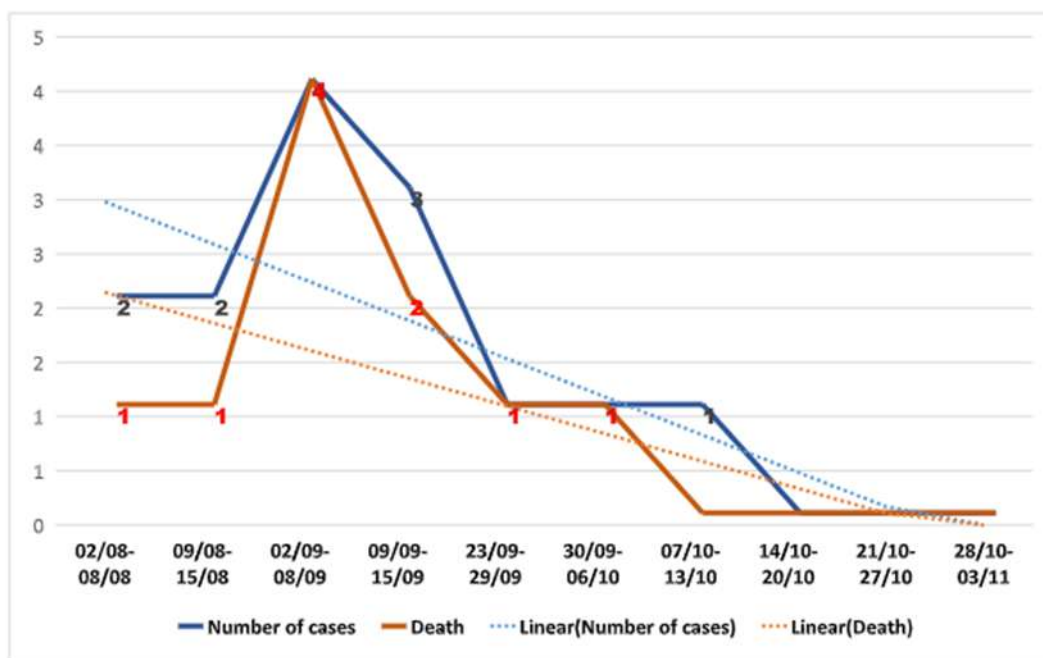
**Table 1: Distribution of clinical presentations by age group**

Clinical Presentation	Age < 2 years		Age [2-8 years [		Age [9-15 years]		Total
	N	%	N	%	N	%	
Isolated Meningitis	3	42,86	3	42,86	0	0,00	6
Isolated Encephalitis	0	0,00	1	14,29	1	14,29	2
Meningoencephalitis	0	0,00	1	14,29	2	28,57	3
Encephalitis + AFP	0	0,00	0	0,00	1	14,29	1
Lymphocytic Meningitis + Cerebellar Syndrome	0	0,00	0	0,00	1	14,29	1
Acute Flaccid Paralysis (AFP)	0	0,00	1	14,29	0	0,00	1
Total	3	42,86	6	85,71	5	71,43	14
<b>p=0,4723</b>							

**Figure 1: Distribution according to geographical origin in Annaba, El Taref and Souk Ahras of reported cases**



Figure 2: Evolution of the epidemic by week of admission



**Figure 3: Distribution according to functional signs**

