CORRESPONDENCE

Early Clinical Experiences With the New Influenza A (H1N1/09)

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Neurological Complications

Winzer et al report early experiences with the new influenza A (H1N1/09) for the time period from April to September 2009. The authors emphasize that the disease course was mostly mild and rarely necessitated inpatient treatment. In most cases—including children—nothing worse than the typical flu symptoms were diagnosed.

We wish to share our own observations of an unexpected rate of neurological complications in 6 hospitalized children (age: 6 weeks to 8 years) infected with the influenza virus A(H1N1/09) in Berlin in November 2009. In addition to flu symptoms (and, in one case, initially gastrointestinal symptoms), the disease manifested, or over the initial 3 days presented, as impaired consciousness levels, somnolence, agitation (in some cases accompanied by hallucinations), and seizures (in 2 schoolchildren who were not of the age when febrile seizures usually occur). One patient had to be mechanically ventilated because of central breathing disorder with apneas/attacks of cyanosis and intermittent hyperventilation ($pCO_2 < 20$ mm Hg). In all patients, influenza A(H1N1)-RNA was confirmed in a nasopharyngeal swab, but not in cerebrospinal fluid (CSF findings [cell count, protein] were normal). Magnetic resonance tomograms of the cerebrum were normal, transient changes of the EEG (retardation) were noted. However, no patient developed any severe pulmonary complications. All were treated with oseltamivir, made a full recovery, and were discharged without any neurological deficits.

As is the case for seasonal influenza (2), children with novel influenza may develop neurological symptoms (3), which—in the presence of normal CSF findings and in the absence of virus in the CSF—can be categorized as encephalopathy. In children with febrile infections and suspected encephalitis/encephalopathy, diagnostic testing for influenza A(H1N1) should be initiated and if infection is suspected, treatment with an antiviral drug (oseltamivir) should be started (3). The parents of children who receive outpatient treatment should be informed of such possible complications and be advised to seek out their doctor immediately.

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Comparison Group Would Have Been Useful

Winzer et al reported their experience with the new influenza virus A(H1N1/09) during the first wave of the pandemic in the summer of 2009 (1). Their hospital clinically examined 3372 suspected cases (including specimens from deep nasal swabbing) on the basis of polymerase chain reaction (PCR). They have contributed fundamental epidemiological and clinical data of the subject. Impressively, only 13% ($n=450$) of swabs were PCR positive.

The authors describe the distribution of sociodemographic and clinical characteristics—unfortunately only for the PCR positive cases (Table, Figures 2–4). For clinical and practice related reasons, a comparison with the PCR negative cases would have been of interest, including the duration of symptoms at the time of the initial contact. The latter is important in interpreting the duration of illness (with or without treatment).

In the article, data on the duration of illness are available only for the cohort treated with oseltamivir ($n=60$). These PCR positive cases were treated in accordance with the guidelines and independently of the severity of their illness by administration of oseltamivir until a negative nasal swab was obtained. “In accordance with the guidelines” implies an approach on the basis of solid data with a high evidence level. However, such data are lacking for both diagnosis and treatment. The cited WHO guidelines are recommendations on the basis of low quality or very low quality evidence (2). In particular, no treatment with oseltamivir is recommended for patients not at risk and with mild or moderate disease. In future, setting up a control group in a randomized study design might therefore be justified. This would put into context the statement that most of the initially symptomatic patients are symptom free after 3 days.

It remains unclear which data the authors used to support their statement “There has not yet been any evidence of oseltamivir resistance.”

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In Reply:

Dr Moßhammer and Dr Eissler point out that we did not include a comparison group in our report of early clinical experiences with the new influenza virus A (H1N1/09). What has escaped their attention, however, is the fact that we did not report a clinical study but our experiences with early cases of the new influenza virus A (H1N1/09) in the summer of 2009. At that time, strict containment strategies were adhered to for suspected cases, but nonetheless, symptom free contacts were also examined. To assemble the latter into a comparison group would not serve the purpose of interpreting the duration of illness. In these early months of the disease emerging in Germany, treatment with oseltamivir followed the guidelines issued by the World Health Organization. If mention is made of guideline conform treatment this does not in any way imply any quality of evidence.

In our article, we reported early experiences with cases of this new disease in Germany, whose course was uncertain at that time. The statement that, at that time, there was no evidence yet of any development of oseltamivir resistance has been repeatedly confirmed in the literature (1).

By contrast, the correspondence by Dr Deindel and Dr Varnholt is an important addition, even though they mention observations that date back only to November 2009. At that point in time, the number of cases of H1N1 in Germany had risen substantially, so that more severe cases were increasingly reported. The neurological complications of H1N1 infections very much deserve consideration.

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Conflict of interest statement

The authors of all contributions declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.