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Original Articles

Post-varicella Arterial Ischemic Stroke in Denmark 2010 to 2016

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ABSTRACT

BACKGROUND: Varicella, most often a benign disease of childhood, is associated with an increased risk of arterial ischemic stroke in children. The aim of the present study was to estimate the incidence of post-varicella arterial ischemic stroke in the Danish child population and describe clinical characteristics of children admitted with post-varicella arterial ischemic stroke. **METHODS:** In the Danish National Patient Register, we identified inpatients 28 days to 16 years of age with a discharge diagnosis of stroke or cerebrovascular disease from 2010 to 2016. Medical files were reviewed, and children with arterial ischemic stroke and varicella infection less than 12 months before onset of symptoms were included. **RESULTS:** We identified 15 children with arterial ischemic stroke and varicella less than 12 months before. In nine children, the diagnosis was confirmed by detection of varicella zoster virus DNA or varicella zoster virus immunoglobulin G in the cerebrospinal fluid. All children were previously healthy, the mean age was four years, and 67% were male. The median time from varicella rash to arterial ischemic stroke was 4.6 months. The most common location of arterial ischemic stroke was the basal ganglia, and affected vessels were most often in the anterior circulation. Fifty-three percent experienced neurologic sequelae of varying degree. **CONCLUSIONS:** In Denmark, where varicella vaccination is not part of the childhood vaccination program, the estimated risk of post-varicella arterial ischemic stroke was one case (including possible cases) per 26,000 children with varicella.

Keywords: varicella zoster virus, varicella, chickenpox, stroke, arterial ischemic stroke, post-varicella arteriopathy, varicella epidemiology

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Introduction

Varicella zoster virus (VZV) is a neurotropic alpha herpes virus that affects only humans. On primary infection, the virus causes varicella, most often a benign disease of childhood.[1] After establishing latency in nerve ganglia along the entire neuroaxis, the virus can reactivate, causing herpes zoster.[2,3] Neurological complications of varicella include encephalitis and cerebellitis,[4] but varicella is also associated with an increased risk of arterial ischemic stroke (AIS) in children.[5-7] The risk of stroke after varicella is reported to be the highest in the first six months after varicella.[7]

Post-varicella AIS in children can be caused by the general effects of infection leading to temporary thrombophilia, but is mainly related to the development of a VZV vasculopathy similar to what has been documented in adults with stroke following herpes zoster.[2] The hypothesized mechanism is direct infection of cerebral arteries by VZV migrating transaxonally from the cranial nerve ganglia to the cerebral arteries where the virus replicates in the arterial wall, causing inflammation and thrombosis.[2] VZV vasculopathy in children is often termed post-varicella arteriopathy (PVA).

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A VZV-related cerebral infarction is usually unilateral and occurs in the vascular distribution of the supraclinoid internal cerebral artery (ICA), A1 or A2 segments of the anterior cerebral artery, or M1 or M2 segments of the middle cerebral artery (MCA). Typical children have experienced a varicella infection less than 12 months before the onset of symptoms and have no other known risk factors for AIS.[2,8] Establishing VZV as the cause of AIS in children can be challenging because the course of disease is often protracted and there may be competing causes of cerebral arteriopathy presenting with similar clinical and radiological findings.[9] In adults, the diagnosis of VZV vasculopathy is considered confirmed when VZV DNA or VZV-specific antibodies are found when analyzing the cerebrospinal fluid (CSF) of affected patients, but some authors maintain that a negative CSF analysis does not exclude the diagnosis in children.[2,10,11]

Varicella is a vaccine preventable disease, and universal childhood vaccination has been introduced in several countries worldwide, with a marked reduction in disease burden as a result.[1] In Denmark, varicella vaccination is not part of the childhood vaccination program. When evaluating possible introduction of new vaccines in the program, severity of the disease is an important factor to consider. Post-varicella AIS is one of the most serious complications of varicella and bears the risk of lifelong disability and increased mortality.[12]

Because the knowledge of post-varicella AIS including the frequency and incidence is still limited, the aim of this study was to estimate the incidence of post-varicella AIS in children in Denmark and describe children admitted with post-varicella AIS with regard to clinical characteristics, treatment regimens, and reported sequelae.

Materials and methods

We utilized nationwide, population-based register data and subsequent review of medical files to retrospectively identify children admitted with post-varicella AIS in Denmark.

Denmark has a population of 5.6 million. Health care is tax-funded and free of charge for all residents. The use of health-care services is registered using the unique civil registration number assigned to all residents. The Danish National Patients Register (DNPR) contains information on all in- and outpatient contacts for all hospitals in Denmark including discharge diagnosis coded according to the International Classification of Diseases, 10th Revision (ICD-10).[13]

In DNPR, we identified all inpatients between 28 days and 16 years of age with a discharge diagnosis of I63-I63.9 (cerebral infarction), I64-I64.9 (stroke), I67-I67.9 (other cerebrovascular diseases), and I68-I68.8 (cerebrovascular disorders in diseases classified elsewhere) between January 1, 2010 and December 31, 2015. This age group was chosen for convenience in order to limit case-finding to pediatric departments. Medical files were reviewed, and patients with first-time arterial ischemic stroke within the study period were identified. Among patients with AIS, we identified and included patients with varicella infection less than 12 months before onset of symptoms of AIS noted in the medical file. Information on basic demographics, time of varicella disease, clinical presentation, brain imaging, and conditions predisposing to AIS (adapted from Amlie-Lefond et al.[14]) and treatment was collected from the medical files of children with AIS and varicella infection less than 12 months before onset of symptoms. Cases of AIS with varicella infection less than 12 months before were regarded as confirmed cases of post-varicella AIS if an analysis of CSF was positive for VZV DNA or VZV-specific immunoglobulin G (IgG). Cases of AIS with varicella infection less than 12 months for whom a CSF analysis was not performed or was tested only for VZV DNA were regarded as possible cases of post-varicella AIS when they fulfilled the proposed definition of PVA: a cerebral infarction in a location consistent with unilateral vascular disease affecting the supraclinoid ICA, A1 or A2 segments of the anterior cerebral artery, or M1 or M2 segments of the MCA, and varicella infection less than 12 months before onset of symptoms in a child with no other known risk factors for AIS.[8]

AIS was characterized by the acute onset of neurological deficit (hemiparesis, altered mental status, seizure, focal neurologic signs) with brain imaging depicting an arterial infarct in a vascular area consistent with the clinical neurological presentation.

Information on neurological (motor or cognitive) sequelae was also collected from the medical file. We reported sequelae as they were described in the medical file at outpatient follow-up visits approximately six months after initial admission for AIS and at last outpatient visit before end of follow-up. Last date of follow-up was on August 31, 2016.

The Danish Microbiology Database is a national database containing results from all microbiologic testing from all Danish microbiology departments.[15] From the Microbiology Database we extracted results of CSF analysis for VZV DNA and VZV-specific antibodies.

From statistics Denmark, we retrieved the number of children in Denmark less than 16 years of age in the middle of the study period for incidence calculation purposes (1,047,189 individuals in the first quarter of 2013).[16] The annual number of varicella cases in Denmark was assumed approximately equal to the size of a birth cohort (≈60.000 children).[17]

Data were analyzed using Microsoft Excel.

Ethical considerations

The study was reported to The Danish Data Protection Agency jr.nr.: 2008-54-0474, and permission to retrieve information from medical files was granted by the Danish Patient Safety Authority jr.nr.: 3-3013-1057/l/.

Results

In DNPR, we identified 191 patients 28 days to 16 years of age registered as inpatients with a discharge code of I63-I63.9, I64-I64.9, I67-I67.9, and I68-I68.9. We reviewed 190 (99%) medical files and identified 81 children with first-time AIS within the study period. Fifteen patients (19% of children with AIS) had varicella infection < 12 months before onset of symptoms noted in the medical file; Figure.

All cases of AIS and varicella infection less than 12 months before onset of symptoms noted in the medical file were regarded as confirmed or possible post-varicella AIS as the diagnosis was either confirmed by analysis of CSF (nine patients) or the case fulfilled the definition of PVA (six patients). One child with confirmed post-varicella AIS was not a Danish citizen and was not included in incidence calculations. Overall, the annual incidence of AIS was 1.3 per 100, 000 children 0 to 16 years of age. The annual incidence of confirmed cases of post-varicella AIS was 0.1 per 100,000 and on inclusion of possible cases of post-varicella AIS, the estimated incidence increased to 0.2 per 100,000 children 0 to 16 years of age. Based on the assumption that the annual number of varicella cases corresponds to the size of a birth cohort and that all cases occur in individuals less than 16 years of age, the estimated risk ranged from 1 of 46,000 to 1 of 26,000 cases of varicella, depending on the applied case definition of post-varicella AIS.

Of the identified patients with confirmed or possible post-varicella AIS, 13 (87%) had a discharge diagnosis of stroke (I63-I63.9 and/or I64-I64.9) in DNPR. Of the patients with a discharge code of stroke, five patients also had a discharge diagnosis of cerebral arteritis or primary cerebral