JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, January 2012, Vol. 57, No. 1
doi: 10.1111/j.1556-4029.2011.01901.x
Available online at: onlinelibrary.wiley.com

CASE REPORT

PATHOLOGY/BIOLOGY

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Sudden Death and Angelman Syndrome

ABSTRACT: Angelman syndrome is a condition characterized by developmental delay due to abnormalities in the maternally derived chromosome 15q11-q13. Typical features include impaired expressive language, an ataxic gait, and seizures. Hyperactivity may result in accidental bruises and abrasions, raising issues of possible inflicted injury. A fascination with water may predispose to drowning. A 5-year-old boy with an established diagnosis of Angelman syndrome is reported who died of upper airway obstruction due to massively enlarged tonsils complicating infectious mononucleosis. Assessment of the severity of underlying illness in developmentally delayed children may be difficult due to failure to vocalize worsening symptoms and distress. In addition, signs of upper airway narrowing due to infection in Angelman syndrome may be masked by the sucking and swallowing difficulties that affected individuals may have with drooling and excessive chewing and mouthing behavior.

KEYWORDS: forensic science, forensic pathology, Angelman syndrome, Epstein–Barr virus, airway obstruction, asphyxia, infectious mononucleosis

Angelman syndrome is a condition characterized by developmental delay that results from abnormalities in the maternal contribution of the chromosome 15q11-q13 genomic region (1). Mutations affecting this area of the chromosome involve the ubiquitin-protein ligase E3A (UBE3A) gene (2). Clinical symptoms include motor impairment, impaired or absent expressive language and speech, ataxia, and seizures. Characteristically those affected are also noted to have a happy demeanor (2).

Cases may come to forensic attention due to medical complications associated with immobility, severe scoliosis, dysphagia, aspiration, and severe epilepsy. There is also believed to be an increased risk of drowning due to a fascination with water. Another problem arises in the assessment of the severity of coincidental medical conditions due to difficulties in communication and examination. The case of a 5-year-old boy with Angelman syndrome is presented to demonstrate an unusual cause of acute upper airway obstruction due to Epstein–Barr infection.

Case Report

A 5-year-old boy with an established diagnosis of Angelman syndrome, with hyperactivity, recurrent respiratory infections, and sleep disturbance, was presented to a physician with fever, cervical adenopathy, and tonsillar enlargement. Additionally, he was noted by his mother to have cyanotic extremities. The clinical diagnosis was tonsillitis and he was begun on oral amoxicillin. Clinical improvement did not occur and he suffered a cardiorespiratory arrest at home several days later. Attempts at resuscitation were not successful.

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Received 17 Aug. 2010; and in revised form 15 Nov. 2010; accepted 20 Nov. 2010.

At autopsy, no overt dysmorphic features were seen. There was no evidence of scoliosis. The most significant findings were in the oropharynx and neck where there was marked bilateral tonsillar enlargement (Fig. 1) associated with prominent cervical lymphadenopathy (Fig. 2). The tonsils were coated with a copious tan-white exudate and were so enlarged that no upper airway inlet was visible. The spleen was enlarged and weighed 247 g (normal = 47 grams) (3). Other findings at autopsy included congested, edematous lungs and focal neuronal dysplasia of the brain. There were no other underlying conditions present that could have caused or contributed to death and there was no evidence of trauma.

Given the findings of lymphadenopathy, tonsillomegaly with significant airway narrowing, and splenomegaly, serum was taken postmortem and sent for Epstein–Barr virus (EBV) serology. This showed IgM antibodies to EBV, with no detection of IgG antibodies to EBV, in keeping with current or recent infection. Microscopic examination of the tonsils and lymph nodes showed benign paracortical expansion with scattered atypical immunoblasts and immunohistochemistry for EBV latent membrane protein (EBV-LMP) showed strong staining in an interfollicular distribution (Fig. 3). There were no oropharyngeal malformations that would have contributed to the upper airway obstruction. Toxicology revealed therapeutic concentrations of codeine, paracetamol, and morphine in keeping with over-the-counter medication. There was also a therapeutic level of clobazam. Death was attributed to upper airway obstruction complicating infectious mononucleosis.

Discussion

Angelman syndrome is a condition associated with neurodevelopmental delay due to a deletion involving the maternally inherited chromosome 15q11-13 (in approximately 70% of cases) (4). Loss of the paternal genetic material at this area results in Prader–Willi syndrome. Other significant genetic findings include 3% of affected individuals with uniparental disomy of chromosome 15, 1% with a mutation in the imprinting center, and 6% with mutations of the

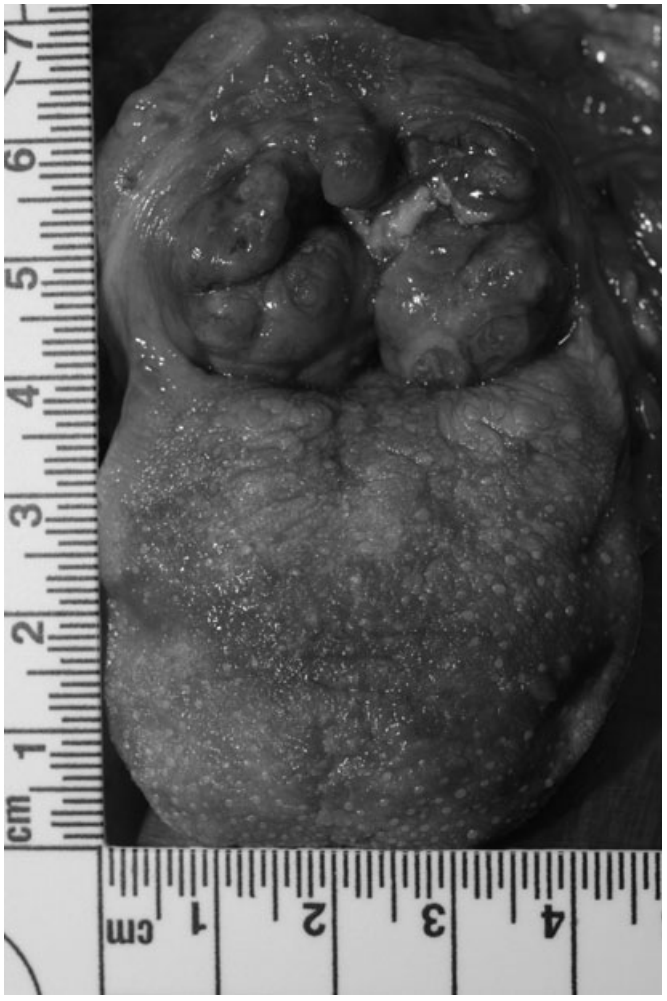

FIG. 1—*The tonsils were markedly enlarged with no visible upper respiratory inlet.*

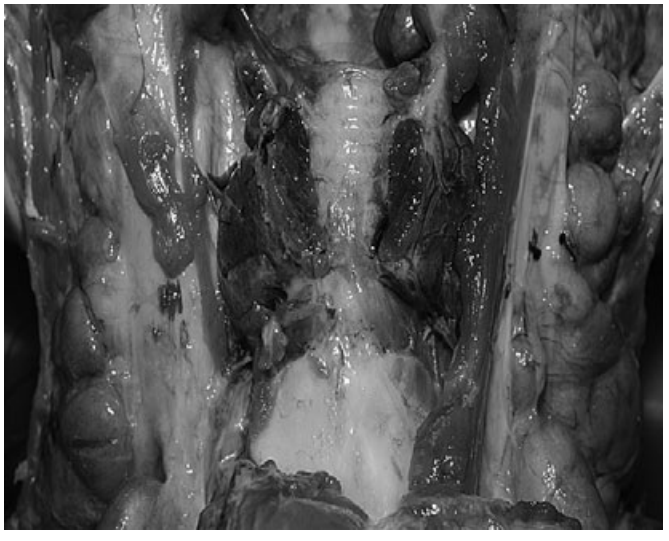

FIG. 2—*There was prominent cervical lymphadenopathy. Note enlarged nodes at both sides of the neck.*

UBE3A gene. Additionally, it is possible to have no detectable genetic abnormality. Most of the genetic abnormalities affect UBE3A gene expression. Recently, studies have shown interaction between the underlying defects responsible for Angelman syndrome and Rett syndrome (5). These syndromes can have significant overlap of clinical findings. The underlying genetic defect for Rett syndrome is on Xq28 (6).

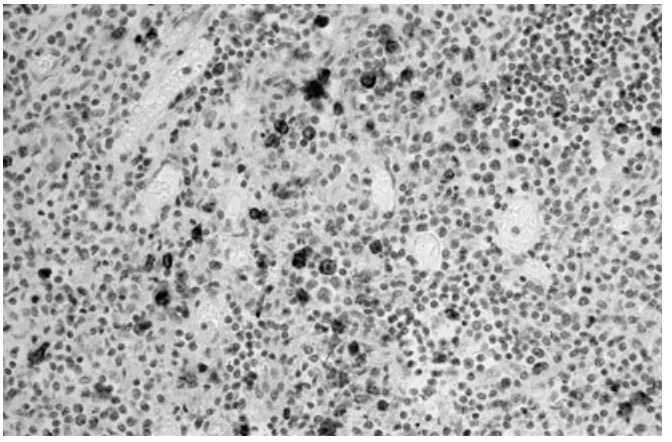

FIG. 3—*Immunostain for Epstein–Barr virus latent membrane protein (EBV-LMP). Section of tonsil demonstrated positive staining in an interfollicular location.*

Typical clinical features of Angelman syndrome may be seen at approximately 6–12 months of age, with the major findings including impaired expressive language, an ataxic gait, and seizures. Typical behavioral patterns include a happy demeanor and a reduced attention span (4). Another frequent behavioral manifestation is hyperactivity, and it has been noted that in extreme cases that constant movement may result in accidental bruises and abrasions, raising issues of possible inflicted injury. Older children also grab, pinch, and bite (4).

Ishmael et al. (7) have reported a fascination with water in individuals with Angelman syndrome with a possible increased risk of accidental drowning. Factors, which may lead to difficulties with water and swimming in particular, include poor coordination, ataxia, reduced muscle tone, and poor cognition (7). The authors emphasize the need for carers to exercise particular vigilance around water or during water-based activities.

Other features that have been reported in 20–80% of cases include a protruding tongue, tongue thrusting, sucking and swallowing difficulties, feeding problems during infancy, prognathia, frequent drooling, and excessive chewing/mouthing behaviors (8). Over 90% of patients have epilepsy, and many different types of seizures occur including refractory epilepsy, atypical absences, myoclonic seizures, and convulsive or nonconvulsive status epilepticus (2,4). The seizure activity may improve during the teenage years (9). Although it has been reported that individuals with Angelman syndrome have a normal life span, the high incidence of epilepsy, with immobility, severe scoliosis, dysphagia, and aspiration (factors that all predispose to respiratory problems), would suggest otherwise (9).

The current case demonstrates an additional problem that occurs with mentally and developmentally delayed children and that is with the assessment of the severity of underlying illness. In the reported case, significant airway narrowing had resulted from tonsillar enlargement due to underlying infectious mononucleosis. In a child with normal mental and physical development, enlargement of the tonsils to the degree demonstrated would result in readily apparent swallowing difficulties. Unfortunately, this may be masked in a child who already has sucking and swallowing difficulties, with drooling and excessive chewing and mouthing behaviors. It is also possible that the speech difficulties associated with Angelman syndrome may also prevent vocalization of worsening symptoms and distress.

EBV is a DNA gamma-herpes virus that infects over 90% of the human population worldwide (10). It is the etiologic agent in infectious mononucleosis and is generally spread between young children by salivary contact (11). Clinical signs of infectious mononucleosis include cervical adenopathy (12), splenomegaly, hepatitis, and pharyngitis. Rarely massive tonsillar enlargement with pharyngeal edema may occur resulting in airway obstruction and death (13). On occasion, upper airway obstruction may be exacerbated by narcotic analgesia (14,15) and so toxicology testing may be a useful adjunct in these cases. The significance of the therapeutic levels of codeine and morphine in the current case is uncertain although it is possible that these may have contributed to airway relaxation. Other causes of sudden death in infectious mononucleosis that were not found in the reported case include splenic rupture, neurological complications, and myocarditis (14).

In conclusion, this case shows that sudden death in children with significant genetic conditions may not be directly related to the defining morphological features of the syndromes. Assessment of the medical status, however, may be complicated by other factors such as reduced cognition, impaired vocalization and features such as difficulties with sucking and swallowing.

Acknowledgement

We would like to thank the South Australian State Coroner, Mr. M. Johns, for permission to publish selected details of this case.

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