Case report

Forensic issues and possible mechanisms of sudden death in Rett syndrome

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Abstract

A 20-year-old female with an established diagnosis of Rett syndrome was found dead in bed. There had been no history of recent deterioration in health and at autopsy no acute lesions were found. There was no evidence of trauma. Toxicological analysis of blood revealed therapeutic levels of carbamazepine and clonazepam. Death was attributed to the complications of Rett syndrome, an uncommon developmental disorder characterized by autistic type behaviour, hypotonia, stereotyped movements, seizures and growth failure, caused by mutations in the MECP2 gene on the X chromosome. Establishing the precise cause of sudden death in individuals with Rett syndrome may be difficult as epilepsy, defective autonomic nervous system control and cardiac arrhythmias may relate more to functional problems rather than to defects that can be demonstrated at autopsy. Thus, although there are a variety of well-documented underlying mechanisms that may cause sudden death in this condition, determining the exact sequence of events in an unwitnessed death may be more by inference and elimination, given the absence of pathognomonic and acute lethal lesions that are able to be found histopathologically. ‘Complications of Rett syndrome’ may, therefore, be the most accurate designation when individuals with this condition are found unexpectedly dead and no anatomical cause of death can be identified at autopsy.

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1. Introduction

A wide variety of genetic conditions are associated with developmental delay and mental retardation. In recent years molecular analyses have enabled the identification of precise loci in chromosomes, where mutations have occurred that result in specific syndromic phenotypic manifestations. These techniques enable greater diagnostic precision and also may lead to family screening in heritable conditions. In addition, the identification of specific entities enables more precise study of clinical manifestations and determination of possible risks for, and mechanisms of, sudden death. It is important that forensic pathologists dealing with cases of developmentally delayed children and adults are aware of possible genetic defects and are able to take appropriate samples for subsequent analyses if diagnoses have not been firmly established prior to death. In the following report a case of sudden death in Rett syndrome is described to illustrate possible mechanisms of death and difficulties that occur in determining the precise sequence of terminal events in this uncommon condition.

2. Case report

A 20-year-old female with Rett syndrome died in her sleep. There had been no preceding exacerbation of symptoms. Her past history included episodic generalized seizures (sometimes occurring two to three times a day) treated with carbamazepine, vomiting associated...
with reflux for which she underwent a Nissen fundoplication, and scoliosis treated with internal spinal fixation. She had recently suffered a fracture of the left tibia. Genetic testing had been previously performed to confirm the diagnosis of Rett syndrome with a characteristic mutation detected in the MECP2 gene on the X chromosome.

At autopsy the body was that of a small adult female with microcephaly and evidence of flexion contractures of the hands, with fixed plantar flexion of the feet. The dermatoglyphs were unremarkable and there was no facial dysmorphism. The spine showed prominent scoliosis with evidence of previous surgery and distortion of both pleural cavities. The heart was structurally unremarkable, with no pulmonary thromboemboli or pneumonia in the lungs. Formal neuropathological examination revealed microcephaly with non-specific mild patchy subpial gliosis, focal neuronal depletion and gliosis in the right hippocampus, mild gliosis of the right parietal cortex and mild bilateral diffuse thalamic gliosis. Toxicological analysis of blood showed therapeutic levels of carbamazepine and clonazepam. There was no evidence of trauma and no other underlying conditions were present which could have caused or contributed to death. Death was, therefore, attributed to the complications of Rett syndrome.

3. Discussion

Rett syndrome, initially labelled ‘weasel’ disease by Hagburg, is a neurodevelopmental disorder primarily of girls characterized by progressive neurological deterioration after an initial period of apparently normal life. The occurrence is usually sporadic, although familial cases may rarely occur. The incidence is uncertain however Rett syndrome has been reported in all ethnic groups with prevalence rates of 1 in 10–20,000 females. Clinical manifestations include autistic type behaviour, hypotonia, loss of purposeful movements of the hands with stereotyped swaying and wringing movements, seizures, gait abnormalities, irregular breathing with hyperventilation while awake, growth failure, scoliosis, reduced abilities to express feelings, avoidance of eye contact and reduced head growth. Osteopenia may lead to limb fractures as in the reported case. Supportive clinical manifestations may include episodic breath holding, bloating from air swallowing, night laughter during sleep, intense staring, bruxism, and screaming spells. There is no characteristic facial dysmorphism. Clinical requirements for the diagnosis of classic Rett syndrome were summarised by the RS Diagnostic Criteria Group with features also being defined for variant Rett syndrome where not all of the usual main or supportive features are present. A preserved speech variant (PSV) exists with unusual feature such as obesity and normal head size.

The syndrome is unusual in that there is not a progressive downhill course as in typical neurodegenerative conditions, but a single period of regression in infancy and early childhood. Four clinical stages have been described: Stage I (early onset stagnation) from 6 months to 1.5 years with delay in developmental progress, lasting weeks to months; Stage II (developmental regression) from 1 to 4 years with loss of acquired skills and mental deficiency, lasting weeks to months; Stage III (pseudostationary) with preserved ambulatory activity but slow neuromotor regression, lasting years to decades; and Stage IV (late motor deterioration) with severe disability and complete wheelchair dependence, lasting decades. Characteristic but not diagnostic electroencephalographic abnormalities are present. Although life expectancy is reduced, with an average age of death of 20 years (range seven to 35 years), a survivor aged 78 years has been reported.

The syndrome was first described in 1966 by Rett, with the genetic basis subsequently found to involve disruption of the gene that encodes for the transcriptional repressor methyl-CpG-binding protein (MECP2) in the chromosome Xq28 region. This is involved in the establishment and refining of synaptic connections. There have been at least 225 mutations identified in the MECP2 gene with the eight most common being found in 70% of Rett patients. The spectrum of presentations is broader than initially thought with asymptomatic females and males being described who have none of the usual diagnostic features but who have MECP2 mutations. Mutations in MECP2 have also been found in females with Angelman syndrome and variant patterns of Rett syndrome, and in males with familial X-linked mental retardation, Klinefelter syndrome and fatal encephalopathy. Once again genotype and phenotype mismatch complicates the assessment of cases and may make the determination of individual prognosis difficult.

Sudden death with no preceding symptoms is a recognised problem associated with the syndrome although the precise aetiology is not always understood. It has been reported in 22–26% of cases compared to 2.3% in the general population of the same age, or a rate of 1.3 per 100,00 in the general population aged between one and 22 years. Possible causes of sudden death in individuals with Rett syndrome are listed in Table 1.

Epilepsy is a manifestation of Rett syndrome with partial and generalized seizures being reported in 50–90% of cases that may certainly be associated with an increased mortality risk. Sudden death in epilepsy (SUDEP) as been defined as the ‘sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus where necropsy examination does not reveal a toxicological or anatomical cause for
death. Although in the reported case the presence of microcephaly and varying degrees of gliosis provided a possible anatomical basis for the epilepsy and thus excluded SUDEP, similar lethal mechanisms may still have occurred. Epilepsy may be difficult to control in Rett patients; for example, in the reported case episodic fitting was still occurring despite therapeutic serum levels of anticonvulsant medication.

The precise mechanisms of death in cases where epilepsy is suspected have also been debated but most likely involve sympathetic-induced cardiac arrhythmia, parasympathetic-induced bradycardia/asystole, apnoea/respiratory failure, a combination of arrhythmia and apnoea, and neurogenic pulmonary oedema with cardiac failure. Alternatively, death in individuals with Rett syndrome and epilepsy may be caused by status epilepticus, airway obstruction/suffocation, aspiration, or trauma or drowning during a fit. Given the lack of pathognomonic findings at autopsy, the only conclusion that may sometimes be made in an unwitnessed death is that lethal epilepsy was a possibility.

Cardiovascular manifestations that may be responsible for sudden death include reduced heart rate variability and prolonged QT intervals reflecting autonomic nervous system impairment that may predispose to lethal ventricular arrhythmias. Further evidence of autonomic dysfunction includes cold hands and feet, gastrointestinal dysfunction and breathing irregularities. Bradyarrhythmias and sinus node dysfunction are alternative possible causes of sudden cardiac deaths in these individuals. No specific anatomical conduction tract defects are, however, demonstrable. Unfortunately, previous ECG recordings were not available for review in the reported case, however significantly longer QT intervals and more abnormalities of T waves have been shown in affected girls than in age-matched controls, with all patients in Stage IV disease having abnormal electrocardiographs. These changes may be due either to central autonomic dysfunction from neuronal changes in the rostral ventrolateral medulla, or possibly to a direct effect of the syndrome on the heart.

Poor autonomic control in individuals with the syndrome may also lead to apneic episodes, which in combination with reduced chest expansion from underlying kyphoscoliosis may predispose to respiratory compromise. This may be exacerbated by episodes of aspiration of gastric contents due to swallowing difficulties from neurologic incoordination, or to pneumonia. Respiratory problems may also lead to problems during anesthesia. Episodic hyperventilation has been reported in 75% of cases and apneic attacks in 70%. Acute gastric dilatation with rupture has also been reported in individuals with autonomic dysfunction and malposition of the stomach due to severe kyphoscoliosis that may be exacerbated by air swallowing. While the manifestations of aspiration, organ rupture and bacterial pneumonia are usually obvious, they may not be recognisable in individuals with severe cognitive and communication impairment. In addition occasional Rett syndrome patients have high pain thresholds, possibly from central defects, that may result in no complaints of pain even after viscus rupture. Thus, these are also possibilities to be checked for at autopsy, despite a lack of history of respiratory distress or discomfort. Other possibilities include pulmonary thromboembolism from deep venous thrombosis of calf veins associated with reduced mobility, or other causes of death that may be completely coincidental to the underlying syndrome.

Inflicted injury must also be considered in conditions such as Rett syndrome given that affected individuals require a high level of care and constant supervision, and may not be able to successfully fend off an attacker. Toxicological studies should be undertaken to determine whether there are lethal levels of drugs that may have caused death, or whether inadequate amounts of anticonvulsant medications had been administered resulting in sub-therapeutic serum levels, thus predisposing to epilepsy.

At autopsy the most obvious findings in Rett syndrome may be of a small individual with evidence of musculoskeletal abnormalities such as scoliosis and flexion contractures of the limbs. Neuropathological examination of the brain is an important step as this may show a small brain with failure of neuronal maturation. Specifically there may be small dendritic trees in pyramidal neurones of layers III and IV of the cortex of frontal and temporal lobes and immaturity of cardiorespiratory neurones in brain stem centres suggesting failure of growth of axonodendritic connections composing the neuropil. Studies have also demonstrated reduced levels of neurotransmitters, including serotonin, noradrenaline, dopamine and choline acetyltransferase. In the reported case there was microcephaly with essentially non-specific neurological findings that may have been secondary to seizure activity.

In summary, Rett syndrome is an uncommon condition that may predispose to sudden and unexpected death from a variety of mechanisms. Confirmation of the diagnosis may be required at autopsy with submission of blood or tissues for molecular analyses. While neuropathological assessment may demonstrate characteristic
features to suggest neuronal immaturity, this is not always the case, and cardiac pathology studies are of limited use. Ascertaining the precise cause of death may not, therefore, be possible due to the insensitivity of standard autopsy techniques in identifying functional neurological and cardiac disturbances.

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References