



Sudden Death in Chromosome 15q11-q13 Duplication Syndrome revised February, 2009

Physician Advisory

Please be advised that there is an increased risk of sudden, unexpected and currently unexplained death among children and adults with chromosome 15q duplication syndrome. The risk is approximately 1% per year. We are publishing this advisory so that physicians can be alert for potentially relevant symptoms and follow-up their patients according to their best clinical judgment with this information.

Description of Sudden Death Cluster

In the 33 month period between April 2006 and January, 2009 IDEAS learned of the sudden, unexpected, and as yet unexplained deaths of six seemingly healthy young people with chromosome 15q duplication syndrome. These young people were described by their parents, therapists, and doctors as lively, energetic, and affected by the cognitive disability, autism, and ADHD that are common with chromosome 15q duplication syndrome. Five of the six young people had recognized seizure disorders. One had no recent seizures, three had seizures that were described as well controlled at the time of death, and one had not had a seizure for over a month.

In this same time period, another five children with duplications of chromosome 15q11.2-13.3 who were medically fragile due to their involved neurological status passed away. Three of these medically fragile children passed in a sudden and unexpected manner.

These cases of sudden and unexpected death involved young people of both genders between the ages of 7 – 26 yrs. All six healthy and two of the medically fragile children died during the night while they were in bed, presumably asleep. Parents reported hearing nothing alarming during the night, including seizure events.

Autopsies that have been performed have been normal at the level of gross pathology, including cardiac and pulmonary examination, and no microscopic pathology has identified a cause of death.

Potential Causes under Consideration

Sudden unexplained death is either due to respiratory or cardiac arrest.

Concerning possible respiratory arrest, the possibility of sleep apnea has been raised. A team from Boston Children's Hospital has reported on sleep study abnormalities in two patients with dup15q syndrome. Each of their patients had generalized tonic seizures; one had associated central apneas with significant hypoxia that occurred with clinical and subclinical electrographic seizures, the other had independent central apneas also with oxygen desaturation, but without temporally related EEG changes.

The second line of inquiry is the possibility of a cardiac event. There are no documented congenital cardiac problems in chromosome 15q duplication syndrome. However abnormal heart rhythm, myocardial infarction, or cardiomyopathy cannot be ruled out. One of the sudden deaths in the medically fragile cohort may have been due to a sudden cardiac arrest, potentially vagally mediated.

Physicians should be aware that mitochondrial dysfunction may be a contributor to respiratory or cardiac arrest. In 2003, Pauline Filipek, MD, published a case finding of mitochondrial dysfunction in autistic patients with 15q duplications (*Annals of Neurology*, 53(6), 801-804).

Management

We do not have sufficient evidence to definitively connect any medication treatment to contribution to any of the deaths. However, 4 of the 5 patients for whom medication history is available were taking medications that are agonists at the GABA-A receptor, either benzodiazepines, phenobarbital, or alcohol derivatives. Such medications are known to be sedating and can be of some risk for patients with respiratory problems, raising concerns about a respiratory cause of death.

This advisory should not be considered a recommendation for anyone to change their treatment without consultation with their physician. It is intended for physicians treating people with chromosome 15q duplication syndrome. Patients with this syndrome often have difficulty to treat seizures and severe sleep problems requiring the use of medications that cause side effects and/or expose patients to adverse events.

However, this is an alert that patients with chromosome 15q duplication syndrome may be at higher risk of sudden death due to respiratory complications of GABA-A receptor agonists, including: benzodiazepines (examples clobazam, ambien, tranxene, librium, Valium or diazepam, Ativan or lorazepam, Klonopin or clonazepam), phenobarbital and related medications, and medications that are ethanol derivatives. Particular caution should be exercised if considering using drugs in this class for sleep or sedation. Please be aware that this is not a documented risk and the risk of changing treatment may be greater than continuation, so each physician will need to weigh risks and benefits carefully. Physicians and families are reminded that changes in these medications should be done under physician directives. We should also keep in mind that these medications should be gradually decreased if they are to be withdrawn to avoid withdrawal syndromes which may lead to serious complications.

Assessments

The IDEAS professional advisory board does not have specific additional assessments to recommend at this time, but doctors should look carefully at each child's medical history (especially any potential respiratory, cardiac or metabolic red flags and overall response to illness), physical examination, and relevant laboratory evaluations. The following additional investigations may be considered (among others):

Cardiac echocardiogram to rule out cardiomyopathy and left or right ventricular hypertrophy, infarct, or wall motion abnormalities, or other abnormal cardiac findings.

Signal averaged electrocardiogram is more sensitive than a routine ECG and is a helpful non-invasive screening tool for increased risk for sudden cardiac death.

A 24 hour heart rhythm ("Holter") monitor may help detect cardiac arrhythmias. It must be stressed that such abnormalities have not yet been identified in this population.

An overnight sleep study with monitoring of respirations, pulse oximetry and EKG (as is done as part of a sleep study or polysomnography) may be considered, either alone or in combination with overnight EEG recording.

Research Resources

Research is underway to investigate sudden death in chromosome 15q duplication syndrome. Several of the families made a brain tissue donation at the time of their child's death. The Autism Tissue Program (ATP) is coordinating the neuropathological exams. Families are

encouraged to consider requesting an autopsy and making a tissue donation at the time of their child's death, whether it is sudden and unexpected or at the end of a more normal life span. Autopsy reports and brain tissue are critical resources for ongoing research efforts. Advance planning for tissue donation and autopsy are strongly encouraged. The Autism Tissue Program is the resource for families wishing to make tissue donations. Families can pre-register with the ATP on their website: <http://www.brainbank.org/>

IDEAS is collecting information from families who pursue additional cardiac, metabolic or sleep studies. Families are encouraged to contact Nicole Cleary, IDEAS Board Chair with their results (normal or abnormal). Physicians can assist in our research efforts by forwarding de-identified patient information to Nicole. It will be forwarded to the IDEAS professional advisory board.

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Final thoughts

Please refer to the IDEAS web site at www.idic15.org for more information about this syndrome and specifically about any additional information that becomes available about sudden unexplained death in this syndrome. IDEAS provides support to families raising children with duplications of chromosome 15q11-13. If you are working with a family who is concerned about sudden death or any other aspect of raising an affected child, you may want to direct them to IDEAS to gain additional support.

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