Autopsy Findings in an Adult with Down Syndrome

Ellen E. Connor, MD, PhD; Ally Darga; Robin R. McGoey, MD

Emergency medical responders were activated to the home of a 59-year-old African-American male in distress and with known Down syndrome complicated by Alzheimer’s disease. He was found to be unresponsive and subsequently became pulseless. Advanced cardiac life support protocols were initiated and continued for two hours in the emergency department. Due to family request, efforts were eventually ceased and the patient was declared dead. Full, unrestricted autopsy examination was conducted under the coroner’s authorization. The cause of death was determined to be a pulmonary thromboembolus in the main pulmonary artery with extension into the bilateral pulmonary arteries. Additional external findings included alopecia universalis, penoscrotal hypospadias, ostium secundum type of atrial septal defect, right ventricular cardiac dilatation, diffuse cerebral atrophy, facial features compatible with Down syndrome, and generalized patches of skin depigmentation over the hands as seen in Figure 1 but also over the feet, lips, areola, and trunk. Microscopic findings included features of pulmonary hypertension. A microscopic image from a section of the thyroid is seen in Figure 2.

What two additional co-morbid conditions can be diagnosed from these images?

Figure 1: (left) External image of the right hand at autopsy showing broad areas of depigmentation. Additional areas of similar depigmentation were seen over the lips, areola, trunk, and both feet. Furthermore, there was no scalp hair, facial, axillary, chest, genital region, or extremity hair. Eyebrows and eyelashes were absent.

Figure 2: (right) Histologic section taken from thyroid at autopsy demonstrating marked glandular infiltration by lymphocytes forming lymphoid follicles containing germinal centers. Thyroid follicles are reduced in number and size, and colloid is depleted. Thyroid follicular epithelium has undergone oxophilic (Hurlhaloid) change characterized by an increased size and abundant granular, eosinophilic cytoplasm (40x, Hematoxylin and Eosin stain).
Down syndrome (DS) is the most common chromosome abnormality among liveborn neonates, occurring in 1 out of nearly every 700 live births. Individuals with DS have a specific combination of phenotypic features that universally includes mental retardation. In 95% of cases, the cause of DS is chromosomal aneuploidy, Trisomy 21, but rare cases of DS can arise from either chromosomal translocation or from mosaicism. DS is characterized by a wide variety of well-recognized dysmorphic features and many, well-known, congenital malformations including congenital heart defects in 40%-50% of cases. Though life expectancy in DS is shorter than that in the general population, survival has improved substantially, with a median age at death nearly doubling over the past 20 years to 56.8 years. As such, awareness of adult-onset conditions and provision of medical services for adults with DS are becoming increasingly important. The patient reported here and the documented findings at autopsy further substantiate the need for a review of the more common pathologic features potentially seen in the adult DS population. A listing of medical problems, and their estimated prevalence, found more frequently in the adult DS population is shown in Table 1.

A wide array of immunologic abnormalities have been associated with DS, including thymic atrophy, susceptibility to infections, and a higher incidence of autoimmune diseases that affect both endocrine (thyroid, pancreas, adrenal) and nonendocrine (stomach, small bowel) organs, including thyroiditis, diabetes, Addison disease, autoimmune hepatitis, primary sclerosing cholangitis, and alopecia areata (occasionally in combination with vitiligo). The link between DS and thyroid dysfunction is well established as the most common endocrine disorder in the DS population. Studies suggest a lifetime prevalence of thyroid disorders on the order of 25%-30%, compared to a prevalence in the general population of less than 2%. The variety of disorders ranges from congenital hypothyroidism to autoimmune thyroiditis, including both Graves and Hashimoto disease. Hashimoto thyroiditis, or chronic lymphocytic thyroiditis, as seen in the current case, however, is by far the most common acquired thyroid disorder in DS and typically causes hypothyroidism with or without detectable serum anti-thyroid antibodies at a median age of onset of 12.3 years and with an equal distribution in both male and female DS individuals.

The link between DS and vitiligo is less well-defined and appears to be tied not only to the concomitant presence of cutaneous alopecia areata (AA) but also to thyroiditis. The milder AA is reported in nearly 9% of DS individuals, while the more severe form of alopecia universalis, as was seen in the current case, is relatively rare at only 2% of DS patients. The mechanism behind the autoimmune predisposition in the DS population has yet to be determined; however, there are two proposed mechanisms that implicate the additional copy of chromosome 21. There is a strong association between autoimmune hypothyroidism and the coding genes for the major histocompatibility complex (MHC) antigens expressed on B cells. While the MHC gene family region occurs on chromosome 6, it is postulated that genes on chromosome 21 participate in the upregulation of the MHC gene complex. The second proposed mechanism involves the autoimmune regulatory gene (AIRE) located on chromosome 21. This gene is selectively expressed in the thymic medulla and is hypothesized to be a protector against organ specific autoimmune disease. Inactivating mutations in the AIRE gene cause the rare autosomal recessive disease autoimmune polyendocrine syndrome type 1, a condition with a similar autoimmune profile to Down syndrome. Despite the additional AIRE gene copy in the DS, AIRE expression has recently been found to be paradoxically reduced in DS.

The current case illustrates many of the comorbid conditions known to challenge the adult DS community, which is

<table>
<thead>
<tr>
<th>Medical Complication</th>
<th>Prevalence in Adult DS Population</th>
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<tbody>
<tr>
<td>Hearing loss</td>
<td>≤70%4</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>50%4</td>
</tr>
<tr>
<td>Congenital Heart Defects</td>
<td>40 - 50%</td>
</tr>
<tr>
<td>Seizures</td>
<td>46% over 50 years5</td>
</tr>
<tr>
<td>Thyroid disfunction</td>
<td>10%-40%6,7</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>10% by 40 years6,7</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>57%8</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>10%10</td>
</tr>
<tr>
<td>Cataract</td>
<td>8%-13%11</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3%12</td>
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Table 1: Reported prevalence of medical complications in adults with DS
expanding due to an improved life expectancy and a community more vigilant health surveillance. The cause of death in the current case is a large pulmonary thromboembolus (PTE). A single case report of a fatal PTE in a postoperative DS adolescent is described in the literature, making the premise of inherent hypercoagulability unlikely. As such, the role that the ostium secundum atrial septal defect played, along with the finding of right ventricular cardiac dilatation and pulmonary hypertension, is unclear but leaves open the possibility for the development of a right-to-left cardiac shunt and subsequent pulmonary arterial thrombus formation. Continued awareness of comorbid conditions in the adult down syndrome population is critical to continuing efforts at establishing practice guidelines and improving care.

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REFERENCES


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