Coclia Pediatric Neck Masses

6. What are the physical findings and clinical features of Pendred syndrome? How do you diagnose?

Cummings:

Pendred Syndrome

The most common syndromic form of hereditary SNHL, Pendred syndrome (PS) was described by Pendred in 1896. The condition is autosomal recessive, and affected individuals also have goiter. The prevalence of PS is estimated at 7.5 to 10 per 100,000 individuals, suggesting that the syndrome may account for 10% of hereditary deafness. The hearing loss is usually congenital and severe to profound, although progressive mild to moderate SNHL is sometimes seen. Bilateral dilation of the vestibular aqueduct is common, and may be accompanied by cochlear hypoplasia. Most cases of PS result from mutations in the \textit{SLC26A4} gene that encodes an anion transporter known as pendrin that is expressed in the inner ear, thyroid, and kidney. Expression of \textit{SLC26A4} has been shown throughout the endolymphatic duct and sac, in distinct areas of the utricle and saccule, and in the external sulcus region within the developing cochlea. Pendrin is thought to be involved in chloride and iodide transport and not sulfate transport.

Affected individuals have thyroid goiter develop in their second decade, although they usually remain euthyroid. Thyroid dysfunction can be shown with a perchlorate discharge test, in which radioactive iodide and perchlorate are administered. Mutations in \textit{SLC26A4} prevent rapid movement of iodide from the thyrocyte to the colloid, and perchlorate blocks the Na/I symporter that moves iodide from the bloodstream into the thyrocyte. The net effect is that iodide in the thyrocyte washes back into the bloodstream in affected individuals, with a release of greater than 10% radioactivity considered diagnostic for PS. The sensitivity of this test is low, making genetic testing the preferred diagnostic method. The hearing impairment is usually prelingual, bilateral, and profound, although it can be progressive. Radiologic studies always show a temporal bone anomaly, either dilated vestibular aqueducts or Mondini dysplasia.

Mutations in \textit{SLC26A4} also cause a type of nonsyndromic autosomal recessive deafness called DFNB4. Whether the phenotype is syndromic or nonsyndromic may reflect the degree of residual function in the abnormal protein. PS and DFNB4 can be diagnosed by screening this gene for mutations. More recently, mutations in the transcription factor \textit{FOXI1} have also been shown to cause PS in patients heterozygous for a mutation in \textit{SLC26A4}.

Emed:

- Pendred syndrome is transmitted in an autosomal-recessive fashion and encompasses a clinical triad of congenital hearing loss, multinodular goiter, and pathologically decreased perchlorate test result.
  - Goiter is not present at birth but rather develops in early puberty or adulthood and is due to abnormal organification of iodine. Pendred syndrome accounts for up to 5-10% of recessive hereditary hearing loss cases. Hearing loss is typically bilateral and most prominent in higher frequencies, often with positive recruitment suggestive of a cochlear site of lesion. A Mondini cochlear malformation and enlarged vestibular aqueduct are often identified.
  - Mutations in \textit{SLC26A4} are commonly identified. The SLC26A4 gene codes of pendrin, a protein that transports chorine, iodide and bicarbonate in and out of cells. The protein is important for the function of the inner ear and thyroid. Genetic testing is available for
mutations in this gene and is indicated in patients with Mondini malformation or enlarged vestibular aqueduct.

7. Name common types of lymphoma in children and treatment regimens (+side effects) for each.

Lymphomas constitute 10-12% of childhood cancers –
   6% NHL
   5% HL

Non-Hodgkin lymphoma

Lymphomas make up a large, if heterogeneous, category of childhood cancers. Chief among these cancers are the NHLs, which are responsible for 6% of all pediatric cancers. NHL is a disease of young children and is more prevalent than Hodgkin lymphoma in the first decade of life; it has an overall predilection for boys, probably because of a subset of T-cell lymphoma. A major factor in NHL is its association with immunodeficiency secondary to underlying genetic diseases, viral infection, or drugs.

Burkitt lymphoma, roughly 40% of all NHL, is associated with EBV infection and endemic on the African continent. Burkitt lymphoma accounts for roughly one half of all incidents of NHL, a number which translates to an incidence of approximately 2-3% among childhood cancers. In its endemic form, the incidence of Burkitt lymphoma can increase as much as 50-fold. Endemic Burkitt lymphoma is associated with EBV and appears to occur in equatorial Africa. Additional environmental factors appear to be at work in the pathogenesis of Burkitt lymphoma because the endemic form differs from even the sporadic form, which can also be found along with EBV in North America as the breakpoints of the 8:14 translocation differ.

Lymphoblastic lymphoma and large cell lymphoma

Comprising 30% of NHL, most lymphoblastic lymphomas resemble T-cell ALL in epidemiological incidence and male predominance, with a constant incidence amongst age groups. No virus or chromosomal abnormality has been associated with lymphoblastic lymphomas. The large cell lymphomas comprise 30% of NHL cases. Anaplastic (30%), diffuse, and mediastinal lymphomas are observed. This variant is associated with EBV in the setting of HIV.

Treatment protocols

<table>
<thead>
<tr>
<th>Phase</th>
<th>Drug</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Cyclophosphamide, vincristine, daunorubicin</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Ara-C, methotrexate</td>
<td>IT</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>PO</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Ara-C</td>
<td>IV or SC</td>
</tr>
<tr>
<td></td>
<td>6-thioguanine</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>IT</td>
</tr>
<tr>
<td></td>
<td>L-asparaginase</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>BCNU</td>
<td>IV</td>
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### Therapy for Lymphoblastic Lymphoma

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cycle</th>
<th>Drug</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance*</td>
<td>1</td>
<td>6-thioguanine</td>
<td>PO</td>
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<tr>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Hydroxyurea</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daunorubicin</td>
<td>IV</td>
</tr>
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<td></td>
<td>3</td>
<td>Methotrexate</td>
<td>PO</td>
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<td></td>
<td></td>
<td>BCNU</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Ara-C</td>
<td>IV or SC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vincristine</td>
<td>IV</td>
</tr>
</tbody>
</table>

Source.—Children's Cancer Group.
Ara-C = cytarabine; BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea, or carmustine; IM = intramuscular; IT = intrathecal; IV = intravenous; PO = oral; SC = subcutaneous.
* A minimum of 5 repeated courses (total duration of therapy >18 mo) are noted. Each course of intrathecal methotrexate (day 0 of each course) consists of 4 cycles of rotating drug pairs that are administered every 2 weeks after blood counts have recovered.

Different places use different protocols

**LSA₂ L₂ protocol**

The LSA₂ L₂ protocol evolved from ALL protocols used at the Memorial Sloan-Kettering Cancer Center in the early 1960s. The LSA₂ L₂ protocol features 3 phases of therapy—namely, induction, consolidation, and repeated cycles of maintenance—given over a total of 2-3 years. Methotrexate is administered intrathecally for CNS prophylaxis throughout treatment. When this protocol was first described, it included irradiation of sites of bulky disease; however, radiation is no longer routinely applied.

**Children's Cancer Group protocol 552**

Between 1986 and 1989, 143 subjects with lymphoblastic lymphoma (10% with localized disease) received treatment with a modified LSA₂ L₂ regimen in a Children's Cancer Group trial (see Table 1). Their 5-year event-free survival was 74%.

**German Berlin, Frankfurt, Muenster treatment protocol**

The German Berlin, Frankfurt, Muenster (BFM) protocols demonstrated excellent results in patients with ALL or lymphoblastic lymphoma. As reported in 1995, 71 subjects with stage III or IV non–B-cell non-Hodgkin lymphoma (see the Children's Oncology Group protocols below) received treatment, as shown in Table 2.

Compared with the LSA₂ L₂ protocol, the BFM regimen adds a re-induction phase and features a less complicated and less intense maintenance phase. In its original report, the BFM protocol included prophylactic cranial irradiation during re-induction. Patients receiving this treatment had a 6-year event-free survival of 79%.

Table 2. Therapy for Stage III and IV non–B-Cell Disease* According to BFM Protocol 86
<table>
<thead>
<tr>
<th>Phases</th>
<th>Drug</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Prednisone, 6-mercaptopurine</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Vincristine, daunorubicin, cyclophosphamide, Ara-C</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>L-asparaginase</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>IT</td>
</tr>
<tr>
<td>Consolidation</td>
<td>6-mercaptopurine</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Methotrexate with leucovorin rescue</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>IT</td>
</tr>
<tr>
<td>Re-induction</td>
<td>Dexamethasone, 6-thioguanine</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>Vincristine, doxorubicin, cyclophosphamide, Ara-C</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>L-asparaginase</td>
<td>IM</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>IT</td>
</tr>
<tr>
<td>Maintenance†</td>
<td>6-mercaptopurine, methotrexate</td>
<td>PO</td>
</tr>
</tbody>
</table>

Source.—Berlin-Frankfurt-Munster Group.

Ara-C = cytarabine; IT = intrathecal; IV = intravenous; PO = oral; SC = subcutaneous.

* Diagnoses included lymphoblastic lymphoma of the T-cell or precursor B-cell type, immunoblastic T-cell lymphoma, and other peripheral T-cell lymphomas. Of note, patients with Ki-1+ anaplastic LCLs were not included.

† Continued until 24 months after diagnosis.
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† Continued until 24 months after diagnosis.

Children's Oncology Group protocols

The most recent Children's Oncology Group phase 3 protocol (A5971) for children with advanced-stage T-cell lymphoblastic lymphoma featured a 4-way randomization between BFM therapy, a Children's Cancer Group modified version of BFM therapy (which did not include high-dose methotrexate/leucovorin during consolidation), and intensified versions of these 2 protocols (with early introduction of daunomycin and cyclophosphamide). Results from this comparison are still pending.

The Children's Oncology Group is developing specific protocols to treat T-cell diseases—both T-lymphoblastic lymphoma and T-cell ALL. In particular, researchers will examine the role of nelarabine (previously known as compound 506U78), a prodrug of the deoxyguanosine analog 9-beta-D-arabinofuranosylguanine (Ara-G) that has shown efficacy in T-cell malignancies.

Rapidly growing or bulky tumors can cause severe metabolic derangement, which may be life threatening. One indicator of the potential for tumor lysis syndrome is an elevated plasma lactate dehydrogenase level or hyperuricemia at the time of diagnosis. The start of effective chemotherapy acutely increases the risk of complications, including hyperkalemia, hyperphosphatemia, hypocalcemia, oliguria, and renal failure.

Pertinent historic information in tumor lysis syndrome (TLS) should include the following:

- Time of onset of symptoms of malignancy
- Abdominal pain and distension
- Urinary symptoms, such as dysuria, oliguria, flank pain, and hematuria
- Occurrence of any symptoms of hypocalcemia, such as anorexia, vomiting, cramps, seizures, spasms, altered mental status, and tetany
- Symptoms of hyperkalemia, such as weakness and paralysis

Physical

Symptoms reflect the severity of underlying metabolic abnormalities.

- Hyperkalemia can cause paresthesia, weakness, and fatal cardiac arrhythmias.
- Uremia can manifest as fatigue, weakness, malaise, nausea, vomiting, anorexia, metallic taste, hiccups, neuromuscular irritability, difficulty concentrating, pruritus, restless legs, and ecchymoses. As uremia progresses, paresthesia and evidence of pericarditis may develop, as well as signs of drug toxicity for administered medications eliminated by the kidney. Features of volume overload, such as dyspnea, pulmonary rales, edema, and hypertension, may develop.
- Elevated uric acid levels may present with lethargy, nausea, and vomiting. Rapidly increasing uric acid levels may lead to arthralgia and renal colic.
- Patients with hypocalcemia may present with carpopedal spasms, tetany with positive Chvostek and Trousseau signs, seizures, anxiety, bronchospasm, and cardiac arrest in extreme cases. Deposition of calcium phosphate in various tissues may be responsible for pruritus, gangrenous changes of the skin, iritis, and arthritis.

Causes
- Tumor lysis syndrome occurs most often in patients with acute leukemia with high WBC counts and in those with high-grade lymphomas in response to aggressive treatment. Tumor lysis syndrome may also occur in other hematologic malignancies and in various solid tumors. It has been reported to occur spontaneously, prior to any form of therapy.
- Those at highest risk have bulky, rapidly proliferating tumors that are sensitive to treatment. An elevated pretreatment lactate dehydrogenase (LDH) level, which correlates with high tumor volume, is a strong indicator for developing clinically significant complications of therapy. Presence of renal insufficiency prior to therapy is also correlated with an increased likelihood of tumor lysis syndrome.

8. Describe the course of 2nd and 3rd arch anomalies with specific relation to pertinent neurovascular structures.

Second branchial cleft cysts
The second branchial cleft accounts for 95% of branchial anomalies, and they are most frequently identified along the anterior border of the upper third of the sternocleidomastoid muscle and adjacent to the muscle. However, these cysts may present anywhere along the course of a second branchial fistula, which proceeds from the skin of the lateral neck, between the internal and external carotid arteries, above the CN XII and IX and into the palatine tonsil. Therefore, a second branchial cleft cyst is part of the differential diagnosis of a parapharyngeal mass.

Third branchial cleft cysts
Third branchial cleft cysts are rare. A third branchial fistula extends from the same skin location as a second branchial fistula (recall that the clefts merge during development); however, a third branchial fistula courses posterior to the carotid arteries above CN XII, below CN IX and pierces the thyrohyoid membrane to enter the larynx, terminating on the lateral aspect of the pyriform sinus. Third branchial cleft cysts occur anywhere along that course (eg, inside the larynx), but they are characteristically located deep to the sternocleidomastoid muscle.

10. Describe the etiology, physical exam findings, and treatment options for cystic hygromas with success rates (hint: surgical and non-surgical treatment).

The term *lymphatic malformation* is a better definition of the lesion that was previously termed *lymphangioma*. Lymphatic malformations are congenital malformations of lymph tissue that result from the failure of lymph spaces to connect to the rest of the lymphatic system. Lesions containing both lymphatic and venous components may be labeled combined venolymphatic malformations. Macrocystic lymphatic malformations (previously termed *cystic hygroma*) contain large thick-walled cysts that have less infiltration of surrounding tissue. Microcystic lymphatic malformations have more extensive infiltration of the soft tissue structures of the head and neck, especially in the tongue and floor of mouth, making their excision difficult.

A lymphatic malformation presents as a soft, smooth, nontender mass that is compressible and can be transilluminated. Typically, lymphatic malformations fluctuate in size as a result of infection or hemorrhage. They mostly impact the cosmetic appearance of the child. Depending on the size and location of the mass, there may be respiratory compromise and difficulty in feeding.

Radiographic evaluation with MRI or CT is invaluable for diagnosis and determination of the extent of the lesion. Radiography shows fluid-filled spaces with surrounding connective tissue. Because these malformations lack a capsule and extend along the lymphatic channels, MRI or CT is essential in defining normal anatomic structures that should be preserved when surgical excision is performed.
The goals of surgery are to improve cosmetic appearance and to counter impaired breathing or eating. Because of the infiltrative nature of these malformations, complete surgical excision is often difficult; debulking of the mass often accomplishes these goals.

Some experts recommend staging of surgical excision in extensive cases. Management with radiotherapy has not been effective. Macrocystic lesions can be treated with sclerotherapy using alcohol. An experimental lyophilized streptococcal compound, OK-432, has been used successfully to sclerose macrocystic lesion.

11. Discuss medical vs. surgical treatment options for cystic hygromas.

Sclerotherapy

Transcutaneous injection of a sclerosant such as alcohol may help decrease a lymphatic VM. It is mostly useful for macrocystic malformations and for combined venous-lymphatic lesions. The procedure is painful; therefore, it is performed by an invasive radiologist under general anesthesia.

Initially, 5 mL of contrast fluid is injected through a venous catheter to delineate the anatomy of the lesion and to detect escape of contrast to the systemic circulation (see the upper left portion of the image below). The upper middle portion of the image below shows injection of contrast into a facial venous-lymphatic malformation. The catheter was relocated when escape of contrast to the facial vein was detected (upper right). When a lumen filled with lymphatic fluid is detected, the lymph is aspirated. Alcohol (100%) mixed with a small amount of contrast fluid (alcohol-to-contrast ratio of 20:5) is then injected through the same venous catheter.

The total amount of alcohol injected into a lesion of a full-sized male is approximately 50 mL. Exceeding a dose of 1 mL/kg is not advised. The catheter is left in place following alcohol injection in case some of the alcohol needs to be withdrawn. Injection is discontinued when skin changes such as peau d'orange, erythema, and bruising are observed. The upper left portion of the image above shows bruising and peau d'orange changes following injection with alcohol of a chest venous-lymphatic VM.

To decrease the swelling, 4 mg of dexamethasone (PO/IV) is administered 3 times every day for 3 days after the procedure. NSAIDs are administered for pain control. The patient usually stays in the hospital overnight for pain control and for monitoring of possible vascular or neurologic limb compromise. Systemic leakage of alcohol may cause myocardial depression. Injection of alcohol close to the skin or mucosa may cause skin slough or skin necrosis. The lower right and left portions of the image above shows necrosis of skin and mucosa following injection of alcohol to the forearm and tongue, respectively.

Bleomycin and OK-432

Intralesional bleomycin and OK-432 have recently been reported to have dramatic results.

Surgical Therapy

Surgery is the only way to "cure" a lymphatic malformation. It should be considered in the following situations:

- When intraoperative and postoperative bleeding can be controlled
- When surgery does not put another organ at risk (eg, injury to the eye or facial nerve)

The surgery must be well planned. Most lesions cannot be resected completely; therefore, the extent of the resection needs to be defined before the procedure. In certain situations, such as eyelid surgery, performing the surgery under local anesthesia is better. This facilitates intraoperative navigation. The image below shows an upper right eyelid lesion before and after resection under local anesthesia.

Lymphangioma circumscriptum is a superficial lymphatic malformation of the skin. This often can be resected completely and the defect reconstructed with a skin graft (see image below). Administration of hemostatic agents such as recombinant factor VIIa (rVIIa) may decrease bleeding and improve surgical efficiency.