Adrenogenital syndrome, where biochemistry meets morphology:

Left testicular biopsies were performed on a 36 year old male with reported endocrine abnormalities and bilateral testicular masses. Both biopsies demonstrated similar results of Leydig cell hyperplasia and abnormal spermatogenesis with “Sertoli cells only”. Since there were endocrine abnormalities in this patient, we inferred that the opposite mass represented Leydig cell hyperplasia as well. Bilateral “Leydig cell tumors” or more appropriately Leydig cell hyperplasia) prompted the question of adrenogenital syndrome (congenital adrenocortical hyperplasia), since true Leydig cell tumors are usually unilateral, in addition to being rare.

At this point in the discussion, I would like to take you back in time to either your college and/or postgraduate biochemistry course(s)…

To understand adrenogenital syndrome, a review of the biosynthetic pathway of steroidogenesis is necessary. Figure 1 outlines the synthesis of cortisol, aldosterone and testosterone via cholesterol. In adrenogenital syndrome, the metabolic abnormality is related to enzyme deficiencies at points in the steroid pathway. Figure 2 highlights the various enzymatic deficiencies associated with this disorder. Of these, 21-hydroxylase and 11 beta-hydroxylase deficiencies are by far the most common. There may be either complete or incomplete expression of the disorder based on the severity of the enzymatic deficiency, the result of a gene abnormality. An exhaustive review of this disorder is beyond the scope of this article and the discussion will be limited to a general description restricted to male patients and the changes observed in the testicular biopsies. In the full blown expression of 21-hydroxylase deficiency, there is a decrease in the production of cortisol and aldosterone, which in turn stimulates the pituitary to produce ACTH. The elevated ACTH can stimulate proliferation of testicular Leydig cells causing Leydig cell hyperplasia) with the subsequent production of excess testosterone. Under normal conditions, the production of testosterone and spermatogenesis are under the influence of luteinizing hormone (LH) and follicle stimulating hormone (FSH), respectively. The elevated level of testosterone causes a reduction in LH and FSH. The absent spermatogenesis in this case may be related to the decrease in FSH levels necessary for normal spermatogenesis or the result of seminiferous tubule outflow obstruction related to the Leydig cell hyperplasia. In Figure 1, the normal biosynthetic pathway is rerouted away from cortisol production toward testosterone synthesis as illustrated by the red rather than blue arrows. In addition, the size of the arrows to the right of the 21-hydroxylase enzyme text-box is smaller than the size of the arrows to the left of the text-box. The size differences are used as a relative illustrative point to highlight the diminished production of cortisol beyond the enzyme defect. The goal of therapy is for replacement of deficient cortisol with normalizing of ACTH levels and subsequent reduction in the selective pressure for the inappropriate production of testosterone.
There is some controversy in the literature in regards to the Leydig cell hyperplasia. Some believe that the “Leydig cells” are actually adrenal cortical cell rests residing within the testicle. The adrenal cortical rests are under the influence of the elevated levels of ACTH and are capable of producing excess testosterone due to the enzymatic deficiency in the steroid synthetic pathway. Morphologically they resemble Leydig cells but don’t have some of the ultrastructural features of “true” Leydig cells. Others believe these cells are modified Leydig cells, responsive to the effects of elevated ACTH levels, but lacking some of the ultrastructural features usually associated with Leydig cells. Images 1 and 2 represent the Leydig cells within the testicle of this patient. These cells contain rich eosinophilic cytoplasm and slightly eccentric uniform oval to round nuclei. In Image 2, the Leydig cells form solid nests within the testicle producing a mass effect. Image 3 represents the adjacent seminiferous tubules. Within the seminiferous tubules in image 4, there are Sertoli cells but no spermatid.
Enzyme Deficiency | Location of Chromosome | Percent or Number of Cases
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21-Hydroxylase Deficiency | Short arm of Chromosome 6 | 90-95% of cases
11-Beta-Hydroxylase Deficiency | Chromosome 8 | 5% of cases
17 –Alpha-Hydroxylase Deficiency | Chromosome 10 | Approximately 100 cases
3-Beta-Hydroxysteroid Dehydrogenase Deficiency | Chromosome 1 | Rare
Cholesterol Side-Chain cleavage enzyme (17,20 Desmolase) Deficiency | | Approximately 50 cases
PSA Screening vs. PSA Diagnostic Lab Testing

There is a lot of confusion regarding the difference between prostate specific antigen (PSA) testing for SCREENING and PSA analysis for DIAGNOSIS. With changes and decreases coming to Medicare reimbursements, we wanted to review the differences between the PSA screening and PSA diagnostic laboratory tests. There are specific restrictions and guidelines that go with each test. Following them will help guarantee payment by Medicare and avoid charges being assigned to the patient. Following these guidelines will also assist in the correct test being ordered the first time and reduce calls from the laboratory to physician office for clarification. This will save time for both the patient and the physician’s office staff, while reducing the turnaround time for the test. It will also decrease the chances of incorrect billing of the patient.

Here are descriptions and guidelines for both PSA tests according to the Centers for Medicare and Medicaid Services.

PSA Screening

- Order only on patients for screening purposes. The patients should not have any signs or symptoms suggestive of prostate cancer.
- Use the CPT code G0103
- Only payable diagnosis code for this test is V76.44 (special screening for malignant neoplasm, prostate).
- It will only be payable by Medicare once every 12 months. If the physician orders more frequently, the patient is responsible for payment.

PSA Diagnostic

- Order only on patients that show signs and symptoms or have had or has prostate cancer
- The CPT code for this test is 84153
- Passable diagnosis codes may range from prostate cancer to most medical conditions
- It will only be payable by Medicare once every 12 months. If the physician orders more frequently, the patient is responsible for payment.

We hope the examples above will assist you in ordering the appropriate PSA tests to match the needs for your patients. For questions or concerns, please do not hesitate to contact me at (919)784-2194.

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Footnote:
The primary author would like to thank his daughter Eileen “aka Ellie” for her help and contribution to the development of this article. Her help was very timely, since she is much closer to college biochemistry than her father, who had to refresh his memory via Lehninger’s Textbook of Biochemistry (copyright 1975 ugh!!!).

References: