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HST.161 Molecular Biology and Genetics in Modern Medicine
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Lecture 2

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy

- increase in mass of heart (i.e. wall thickness)
 - o there's a round or two of cell division in the heart after birth, but then it's over – heart muscle is terminally differentiated
 - o the heart doesn't actually ever seem to get cancer (no cell division)
- myocyte mass (increase)
- interstitial content
- risk for poor prognosis from CV disease
- risk for heart failure

Hypertrophy is usually secondary to another cardiovascular disease or condition, often acquired from having this other disease (when the heart has to work too hard to compensate for the problem, it will “bulk up”)

- examples: hypertension, aortic stenosis, diabetes, myocardial infarction

Physiologic hypertrophy: people who are vigorously training can experience cardiac hypertrophy, but this is a normal physiological response. This is an appropriate response because if you turn off the stimulus, the response will go away.

It's not well-understood how the condition goes from physiologic to pathologic. (This virtually never happens in an athlete).

Hypertrophy occurs in the general population at a rate of 2-4%, people who've never had a previous serious cardiac condition.

- there are some populations that are at higher risk, which suggests that some determinants may be genetic
- can be clustered in families; suggests Mendelian form of inheritance
- it's been assumed that development of cardiomyopathy is a complex variance in genes; the Mendelian inheritance patterns are helping to inform these hypotheses.

Problem due to hypertrophy: cavity volume is reduced – especially of the left ventricle

Heart responds in two different ways to changes: hypertrophy (growth of heart muscle mass) or dilating (increase in chamber size/cavity size – like a balloon); today we're focusing on hypertrophy.

Inherited form: histology is very different from normal; in a normal heart, uniform linear alignment of interstitial matrix and myocytes. In hypertrophic heart, orientation of myocytes is abnormal and in disarray (cells oriented every which way). Cells also die prematurely; interstitial necrosis followed by fibrosis increases.

Historically, there are many records of hypertrophy but it's often called different things. Technology was much more limited; you could do crude X-rays, or palpate the heart, to tell that something was wrong.

Clinical features of HCM:

- inherited (autosomal dominant) or sporadic
- age-related penetrance of hypertrophy (genetic predisposition; age-related penetrance is actually the norm for developing genetic diseases, yet the age dependency is something that's often kept us from realizing genetic involvement)
- variable severity/distribution of hypertrophy (hypertrophy can occur in different places within the heart)
- Symptoms:
 - o absent (no symptoms for a very long time)
 - o Dyspnea (shortness of breath)
 - o Angina
 - o Palpitations (arrhythmia)
 - o Syncope (fainting)

Natural history:

- insidious progression
- atrial enlargement
- arrhythmias
- heart failure (lack of normal systolic function; or lack of diastolic function)
- sudden death

Clinical diagnosis:

- physical exam
 - o abnormalities of cardiac rhythm (ventricular extra systoles, atrial arrhythmias)
 - o cardiac murmurs
- electrocardiogram
- 2-dimensional echocardiogram

EKG introduction: contraction begins at SA Node, propagated to AV node where there is a physiological cause; then impulse is dissipated through ventricle. These electrical impulses can be detected and measured with an EKG. EKGs can show irregular rhythms and differences in the amount of current; a larger current probably reflects a larger heart.

A septal bulge – increased mass obstructing exit of the blood into the aorta – accounts for mistaken diagnoses of aortic stenosis. Today we treat this by removing some tissue, via a myectomy.

HCM Pathophysiology:

Primary:

- preserved (enhanced) systolic function
- diminished relaxation (diastolic dysfunction)

Secondary:

- arrhythmias

- heart failure

Only treatment for heart failure is a transplant.

[Patient talk]

Genetic Linkage: independent vs. dependent assortment during meiosis (depends on whether the genes are physically close together in the DNA)

Pedigree showing Aa: A is clearly not the right gene for your disease.

Linkage to a known gene helps us determine the location of the gene actually responsible for the disease, but doesn't tell us the identity of the gene.

Single nucleotide substitution was found in the gene coding for the beta-myosin heavy chain gene, in one family with HCM. Looking in other families, however, different mutations were found; common across them, however, they found that there were mutations in proteins involved in the contractile function of the sarcomere (in the heart; this particular myosin is heart-specific). The specific location of the myopathy within the heart is partially dependent on environment.

This isn't **always** the gene; about 25% are something else. Took the people who didn't fall into the first group and did linkage studies with their families.

- AMP kinase gamma-2 subunit mutation causes constant activation of a complex that increases levels of ATP and cardiac glycogen

HCM mimic: LAMP2 mutations (lysosome associated membrane protein 2)

- X-linked
- Massive LV hypertrophy in heart
- Refractory arrhythmias
- Rapid heart failure progression
- Often with muscle, CNS, hepatic disease

Looked at HCM in children and in the elderly populations:

Some children exhibited de novo mutations!

Some children's parents had the disease too, but it wasn't recognized clinically.

And in other cases of something looking like a new mutation – it's because the child's father isn't really the father.

There are dozens of different mutations possible in the myosin and actin molecules that will cause HCM.

Location and severity of the hypertrophy doesn't seem to be dependent on the genetics.

- Mouse models show that the exact same mutation doesn't create the exact same morphologies.
- What correlates with arrhythmias? The amount of hypertrophy itself.

How do mutations affect sarcomere function?

- HCM mutations seem to create “super” myosins (in a heterozygote, half the proteins are normal and half are mutated)

Why are these hearts bad rather than “better”?

- We’re not sure; they might burn out sooner? But that doesn’t really make sense; e.g., athletes don’t tend to die sooner than couch potatoes.
- Supply and demand: metabolic contributions may have something to do with it, but it’s very hard to test these hypotheses.
- Calcium cycling? Myopathic mice hearts are activated at lower Ca^{2+} concentrations; SR Ca^{2+} and Ca^{2+} binding proteins are decreased in HCM hearts. The mutation may be trapping Ca^{2+} in the sarcomere, which doesn’t let the heart relax as robustly as it should. Using Ca^{2+} blockers *from birth* restores diminished Ca^{2+} binding proteins and decreases the amount of hypertrophy (but this doesn’t work after hypertrophy has been established).