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Notes From Cardiology Clinic: Brittle Bones and Blue Sclerae

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The intern on the phone said: “We’ve got this kid down in Emergency with no blood pressure, and he’s sitting here talking to us like nothing is wrong.” It was 1973, and I was a cardiology fellow at Emory University in Atlanta, covering the acute cardiac units that evening at Grady Memorial Hospital.

He was 22 years old and had osteogenesis imperfecta: the blue sclera, the brittle bones, and other features of the syndrome, including a triangular face, hyperextensible joints, and a mild clotting abnormality. He came from a small town in rural Georgia, where he had defied his condition by playing quarterback on his high school football team. He was too small for football anyway at 66 inches and 125 pounds, even without considering the risk of broken bones. Between the ages of 15 and 16 he had sustained 6 fractures.

Osteogenesis imperfecta covers a wide spectrum of clinical severity ranging from death in utero to only mild bone abnormalities and a normal lifespan. A 1979 classification defined 4 types, from mild to lethal, based upon clinical and radiographic features. At least 17 different genetic defects have now been identified, including 8 that are autosomal recessive, although the most common one is autosomal dominant with variable penetrance.¹ A functional classification groups the genetic abnormalities into 5 categories: (1) defects in collagen synthesis, structure, or processing, (2) defects in collagen modification, (3) defects in collagen folding and cross-linking, (4) defects in bone

mineralization, and (5) defects in osteoblast development with collagen insufficiency.¹

Nowadays bisphosphonates are widely used to treat osteogenesis imperfecta, with the goal of increasing bone volume, even if bone quality is still impaired. Whether this therapy reduces long bone fractures is uncertain because the number of subjects included in placebo-controlled trials is small (n=424).¹ Aortic and mitral regurgitation are the most common cardiac abnormalities seen in this condition. In one echocardiographic study 10% of adults with osteogenesis imperfecta had severe and 10% had moderate aortic regurgitation, while 7% had moderate mitral regurgitation.²

I don't remember all of the details of my patient's history, but can refer back to the published case report.³ A heart murmur was heard when he was 15, and 3 years later he gradually developed exertional dyspnea and fatigue, followed within a year by orthopnea. Physical examination at that time suggested severe aortic and mitral regurgitation, and this was confirmed by cardiac catheterization. He underwent aortic and mitral valve replacement, complicated by prolonged oozing that required reopening his chest.

One year later he developed progressive cardiomegaly, without symptomatic deterioration. A repeat catheterization showed that his valves were functioning normally, but levophase filming after a pulmonary artery injection showed left ventricular dilatation and

dysfunction so severe that the ejection fraction could not be calculated. He returned to his previous level of activity and denied all symptoms except dyspnea on exertion.

It was 9 months later, 21 months after surgery, when he walked into the Emergency Department complaining increased dyspnea, fatigue and edema. I was confident that with meticulous, tailored therapy I could improve his heart failure. I worked to optimize his oxygenation, his hemoglobin level, his heart rate, his preload and afterload, and to reduce the work of breathing. I used inotropes carefully, beginning with small doses. I stayed at his bedside, making adjustments minute to minute.

He talked about his family, his girlfriend, his hopes and plans for the future. He did not mention osteogenesis imperfecta or anything else about his medical circumstances. In response to questions as to whether he was warm enough, was his breathing better, did he have pain anywhere, the response was always the same: "I'm OK." Our corner of the ICU seemed unusually quiet with just me, my patient, and a very competent nurse. As the night wore on, it became increasingly obvious that he was not getting better. After midnight he became quieter, and then somnolent. He passed away 8 hours after admission. Nothing that I had done had influenced his clinical course in any meaningful way.

Treatment of acute heart failure in 1973 was based upon faulty assumptions, and sometimes caused more harm than good. One area of research was focused on finding a measure of contractility in animals or patients that was independent of loading conditions.⁴ Maximum dp/dt during isovolumic contraction, and v_{max} , defined as the theoretical maximum velocity of contraction, were oft discussed possibilities. The idea was that such a measurement would allow a better assessment of inotropic drugs, and the future was bright because such drugs were under development.

Beta-blockers had become available in the late 1960's and were enthusiastically embraced for the treatment of angina and some arrhythmias. Beta-blockers were avoided in patients with heart failure, and if a patient with even a hint heart failure needed a beta-blocker for angina, digitalis was sometimes given concomitantly. It was thought that elevated catecholamine levels preserved cardiac output in compensated heart failure, and that blocking them invited disaster. The notion that beta-blockers would be safe and effective treatment for heart failure would have been met with incredulity by any cardiologist in that era.

So, our approach to heart failure was 180 degrees wrong. Not that it would have made a difference to my patient at the time I saw him. Our approach to sudden cardiac death was to focus on the eradication of ventricular arrhythmias with anti-arrhythmic drugs for

high-risk patients, and that turned out to be very wrong as well.⁵

Misdirected therapies occurred in other branches of medicine also; for example, peptic ulcer disease was treated for decades with vagotomy and pyloroplasty when the cause was *H. Pylori* infection.

Are we making any huge mistakes like this in modern cardiology? We have accumulated so much knowledge. We have an array of precise imaging techniques. We have a multitude of carefully conducted clinical trials that form the basis for well-considered guidelines. Surely we know what we are doing now.

Sometimes I think back with wonder and admiration to a teenage boy with osteogenesis imperfecta playing quarterback for his high-school football team, long ago, in rural Georgia. He must have felt like such an outsider because of his genetic condition, but as quarterback, he could belong.

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