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The Genetics of Spinal Disease

THE JOURNAL OF THE SPINAL RESEARCH FOUNDATION
A multidisciplinary journal for patients and spine specialists

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"The Genetics of Spinal Disease"

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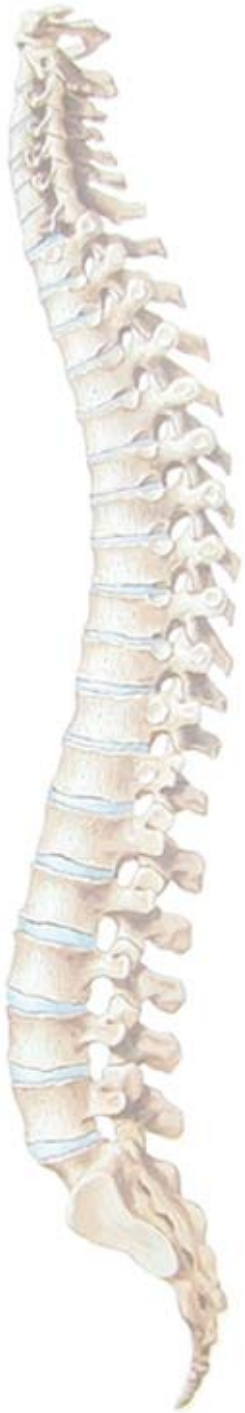


From the Editor

Brian R. Subach, M.D., F.A.C.S.

Genetics and Spine Disease: Lessons from the Twin Spine Study

Much of our understanding of spinal disease has been based on the thought that degeneration of the spinal discs was a result of the aging and progressive wear and tear process of repetitive mechanical insults and injuries. Research to this point has focused on these mechanical factors as the primary causes of degeneration of the discs. Most of our preventative efforts, as well, have focused on limiting stress on the spine in order to minimize damage. As a result of new groundbreaking information, which has come to light through a recent study, it is entirely possible that degeneration of the spinal discs may be viewed as a genetic disorder with environmental factors playing an important role in progression.

The recent Twin Spine Study, a multidisciplinary international research program, actually evaluated the progression of spinal disc disorders. The premise of the study states that two twins will have identical genetic composition, however, they may be exposed to dramatically different environmental factors. If truly there is a genetic link to the development of spinal disc degeneration, then the twins should have the identical disease process irrespective of the contribution of environmental factors. Specifically, the Twin Spine Study began in 1991 when researchers from both Finland and the United States initiated a pilot study looking at twenty pairs of identical twin siblings who differed only in the environmental exposure to tobacco. One of the twins essentially was a heavy smoker, the other was not. Magnetic resonance imaging studies demonstrated similar disease patterns. Since that time, the Twin Spine Study has grown to include three hundred sets of identical twins as well as fraternal twins. Over the past few years, collaborators from both Canada and the United Kingdom have begun to participate. At this point, the entire sample population includes multiple pairs of twins which in some cases were discordant based upon behavioral activities (such as smoking) or environmental factors (such as heavy physical demands of work, routine exercise participation, or even occupational driving). Each of these variables may independently contribute to spinal disc degeneration and back pain. Through a series of interviews, physical examinations, clinical tests and radiographic studies each of the participants were thoroughly evaluated. MRI scans were performed and DNA was extracted from blood samples taken from each subject.

Looking specifically at the risk of lifetime driving hours, forty-five pairs of identical twins were evaluated. One of the twins in each case would have a significantly higher number of lifetime driving hours than the other with the hypothesis that the vibration from prolonged driving and the sedentary position associated with driving would increase the stress on the lumbar spine. MRI scans obtained on these patients demonstrated no significant evidence of greater disc degeneration in the driving population. As a result of this and other cohorts within the study, researchers were lead to further investigate the genetic link. The first notable finding was that disc degeneration and back pain were clearly not the same, meaning that the perception of back pain may be mediated through a genetic link and the appearance or presence of degenerative spinal disc disease may be mediated through a separate genetic link. Obviously, the complexity of the degenerative process, as well as the complexity of pain perception, requires further investigation.

In summary, disorders of the lumbar spine and back pain in general afflict most developed countries of the world causing significant health care costs and lost work time. Current prevention and treatment strategies have demonstrated only modest effects of altering the disease process. Because the underlying pathologic process and the risk factors which lead to degeneration are largely unknown, most of what we understand and believe has been developed over a significant period of time. We are yet to understand the specific pain mechanisms which trigger discomfort in one patient, while an identical MRI scan may not be associated with any discomfort in another patient. In any case, simply adhering to a model of repetitive wear and tear causing disc degeneration alone is not tenable. The Twin Spine Study leads us to believe that, despite

From the President

Thomas C. Schuler, M.D., F.A.C.S.

Impact of Genetics on Spinal Health Care

Patients often ask what they can do to avoid painful spinal conditions caused by disc degeneration. My answer to them is simple: they need to do a better job of picking their parents! Genetics is probably the most significant risk factor for disc degeneration and the development of painful spinal conditions. Research has revealed that individuals with a family history of spinal problems are more likely to have spinal problems.

This is something we commonly see in the clinic on a daily basis. A patient will state that he/she experiences a problem which his/her father or mother had at the same age.

The overall prevalence of painful spinal degenerative conditions is enormous in our society. Eighty to ninety percent of people have severe neck or back pain at some point in their adult life. Environmental factors (such as nicotine use, obesity, de-conditioning, poor ergonomics and occupational factor) contribute to the onset of disc herniations and disc disruptions as well as neck and back pain. Traumatic events often are the stressors that create a patient's symptoms. However, without an underlying genetic risk factor, many spinal problems would not become symptomatic or would resolve more rapidly.

From the Editor (continued)

environmental factors, there is clearly a genetic link to disc degeneration.

The role of genetics in spine disease is the main topic of the Spring 2009 issue of the Journal of the Spinal Research Foundation. Articles in this issue provide an overview of the genetics of the spine and discuss the role of genes in conditions such as degenerative disc disease, scoliosis, and congenital malformations of the cervical spine. Further articles also review the emerging gene therapies and their potential for spine disease. Overall, this issue of the Journal presents information and promotes an understanding of a crucial aspect of spine disease.

A new area of research is embarking on the concept of genetics as a predictor of pain perception. This area of research investigates why people perceive pain at different intensities for relatively similar levels of stimulus. Genetic predisposition is probably a significant factor in how one's body perceives pain and is able to function with that pain. This would explain why two patients with identical problems will often experience dissimilar clinical courses. This also explains the difficulty in making treatment decisions for two individuals with the same problem: a physician may see entirely different responses to equally well-performed operations on these two individuals. The bottom line is that some people handle pain well and others do not. Psychological overlay is also an important element in pain perception. Psychological overlay is the result of genetic factors as well as environmental factors.

Genetics is clearly a significant factor on many levels and the one that, to date, we have no control over. Future areas for the advancement of spinal health care may include genetic testing as a way to better predict successful non-operative and surgical treatment outcomes. With a better understanding of genetically induced limitations and a patient's ability to recover from intervention, surgeons can more carefully select the patients who will benefit from appropriate intervention. Clearly this leads to many ethical dilemmas which will require extensive evaluation and consideration.

So, when patients ask how to avoid neck and/or back problems my advice to them is:

(1) simply avoid nicotine,
(2) maintain appropriate body weight and proper nutritional intake,
(3) maintain a proper core strengthening program, flexibility program and aerobic conditioning program
(4) use proper ergonomics in daily activities and work activities and
(5) enjoy life.

Until we can choose our genetics, this list will have to suffice for now.

Ask the Expert

Christopher H. Comey, M.D., New England Neurosurgical Associates

Will a spinal fusion cause damage to the adjacent levels of my spine?

Dr. Comey: That is an excellent question. In a single-level fusion, there is little impact on the spine. In a multilevel fusion, the major concern is adjacent-segment degeneration. Discs act as mechanical shock absorbers between the vertebrae. When the spine is fused, the discs above or below the fusion may absorb the sheer forces of everyday motion and thus wear out prematurely. When a fusion surgery is performed, it is essential that overall spinal balance is maintained. If this is done, the adjacent segments are at less risk of degeneration. Also, certain minimally invasive techniques and approaches do less damage to the supporting structures of the spine.

The doctor told me that he would be taking bone from my hip or pelvis to perform my surgery, are there any alternatives?

Dr. Comey: This is a great question and one that I am faced with on a daily basis in the office. There are three other choices: donor (cadaver) bone, synthetic spacers or biologics. The donor bone, also called allograft, may be frozen or freeze-dried to sterilize it prior to implantation. It has a reasonable rate of healing, but not as good as your own (hip/pelvis) bone. There are other synthetic bone choices that are man-made, but these usually require some of the patient's own bone as well. In 2002, the FDA approved a bone protein called rh-BMP-2, or recombinant human bone morphogenetic protein 2 (often shortened to simply BMP), which actually stimulates new bone growth. This naturally occurring human protein is manufactured, placed on a collagen sponge, and attracts bone forming cells from surrounding tissue to stimulate new bone formation. It has a very predictable pattern of bone growth and has tremendously improved fusion rates. Not only does this represent a very exciting advance in spinal healthcare, but it is also the first application of genetic engineering in our field.

How did I herniate my disc?

Dr. Comey: Most of the time, there is no specific single causative event. Most spinal specialists believe that disc degeneration is a gradual process of deterioration due to repetitive stresses. A herniated disc is simply a fatigue response of the outer lining of the disc (annulus) with a fragmented inner cushion (nucleus) occurring over years of wear and tear. This does not mean that an isolated event cannot directly harm the disc. Rather, poor posture and bending/lifting activities are the most common culprits in disc herniation.

What causes neck pain?

Dr. Comey: Neck pain has a variety of causes. Poor body mechanics, herniated discs, spinal fracture, muscle spasms, spinal deformity, and osteoarthritis are a few reasons. Your physician can determine if the pain is mechanical, (coming from the joint or the disc); radicular, (coming from a compressed nerve or nerve root); or myelopathic, (coming from the spinal cord) and determine a treatment plan.

Christopher H. Comey, M.D.

Dr. Comey is Chief of Surgery at Holyoke Medical Center. His practice encompasses all aspects of neurosurgical care with a special emphasis on minimally invasive surgical techniques and the treatment of complex spinal disorders. Despite his commitment to his patients, he also finds time to pursue his research interests and to lecture to surgeons around the country.

Dr. Comey has authored over a dozen peer-reviewed publications as well as contributed to a number of textbooks on diseases of the spine.

Dr. Comey is an active member of the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, the North American Spine Society, the Joint Section on Disorders of the Spine, the Massachusetts Medical Society, and the Hampden District Medical Society.

Spine Tale

Theresa Scott is our Spinetale for this edition of the Journal of the Spinal Research Foundation. When Theresa first arrived at the Virginia Spine Institute in August 2008, she had been having low back pain for more than a year. The low back symptoms seemed to be insidious in onset. She was having pain across the lowest part of her back in a horizontal fashion and the symptoms had clearly worsened over time. She had been previously very active and athletic throughout her life, and began having low back pain as well as symptoms into both legs which were making it difficult for her to perform not only her work-related activities but also her personal activities. Theresa was a busy executive for a mortgage banking firm. It was becoming increasingly difficult for her to simply sit at a computer without pain.

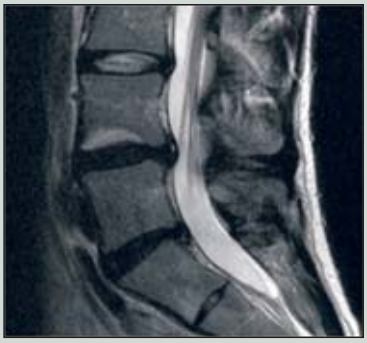

Theresa Scott

Eighty percent of her pain was in the low back while twenty percent of her symptoms were in the lower extremities, mostly manifest as numbness in the back of the thighs and back of the calves. When asked to give a pain score between 0 and 10 she stated that her average daily pain was a 6. Many times the numbness in the posterior thighs and calves would also be accompanied by pain as well. Her symptoms seemed to worsen with activity throughout the course of the day. Many times simply rolling over in bed would awaken her from sleep. Her most comfortable position was simply lying on her back with her knees bent. Clearly her symptoms became worse with bending and lifting and in general she had difficulty bending, lifting, walking and performing most of the activities of her daily life, even on the weekends.

She had previously tried anti-inflammatory agents, narcotic pain medications physical therapy, exercise therapy activity modification, rest and epidural steroid injections into her lumbar spine. None of these treatments seemed to help. ; She had no significant medical history or significant traumatic injuries and no family history of spinal disorders. She did not smoke or drink alcohol. In general, for thirty-nine years of age she was in excellent health. Why would her back be failing at this point?

In August 2008, she was having tenderness over her lumbar spine, specifically at the L4, L5 and S1 levels. Her back hurt when she bent forward. Her back hurt when she bent backward. Everything seemed to worsen her pain. Her sacroiliac joints seemed to be restricted on both sides and were incredibly painful. The reflexes in her legs were symmetric, but she clearly had evidence of weakness in the left ankle muscles, which often indicates compression of the sciatic nerve. Sensory examination demonstrated no significant numbness to light touch or pinprick testing; however, she still had these feelings of a numb sensation into the back of the thighs and calves.

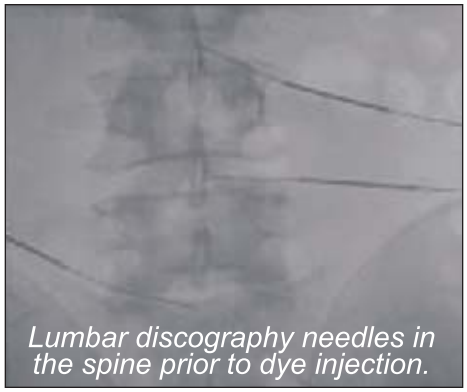
Her MRI scan demonstrated evidence of degenerative changes at both the L4/5 and L5/S1disc spaces. At L4/5, the disc space had lost approximately twenty percent of its normal height, while at L5/S1 eighty percent of the disc was gone. The bending x-rays that she performed demonstrated segmental instability, in which collapse of the disc results in loosening of the supporting ligaments and actual wobbling of the vertebral bodies.


MRI scan of the lumbar spine showing severe degeneration in the lowest two discs, L4/5 and L5/S1.

She was frustrated by her inability to improve with physical therapy and other conservative strategies and therefore underwent a lumbar discography in an attempt to identify a clear cause for her pain. During the discography procedure, the physician places small needles into each of the disc spaces and then injects a small amount of dye in an attempt to stretch the disc. In a normal disc, this typically produces a pressure sensation. In a failing disc, this will often provoke a patient's typical low back discomfort. During Theresa's discography, she felt immediate, severe and familiar

Spine Tale

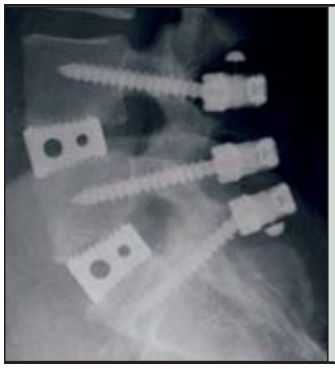
low back pain radiating down both legs when the dye was injected at the L4/5 level. At the L5/S1 level the injection caused a more moderate diffuse low back pain which was very familiar as well. In summary, she had two levels of symptomatic disc degeneration.



Lumbar discography needles in the spine prior to dye injection.

Since non-operative strategies had failed to this point, Dr. Brian Subach discussed with her the options for surgical intervention, including the possibility of artificial disc surgery or fusion surgery. Based upon her imaging studies and her evaluation, she decided that she would pursue fusion surgery. On September 29, 2008 she underwent a two-hour procedure to remove the diseased discs from the front of the lumbar spine. Essentially, through a C-section type incision, Dr. Subach was able to remove the degenerative discs and replace them with two titanium fusion cages (LT-cages) filled with recombinant human bone morphogenetic protein (rh-BMP-2). Two days later, she was taken back to the operating room for fusion along the side of her spine as well as placement of stabilizing screws into the spine using a connecting rod made out of plastic (poly-ether-ether-ketone (PEEK)). Essentially, adding stability to her spine without the painful rigidity of typical titanium screw-rod constructs. Flexible rod technology is at the forefront of spinal instrumentation. The instrumentation provides adequate stabilization in extension (back bending) while decreasing the risk of sacroiliitis (inflammation of the pelvic joints) and adjacent segment degeneration (arthritis marching up the spine to the next level).

After surgery, she was clearly uncomfortable. She was taking pain medications and quite sore for the first weeks. When she was seen back in the office two weeks after surgery, she stated that her pain level was 2 on the pain scale of 10 compared to the 6 which she was prior to surgery. Obviously, she was still taking medications and just starting physical therapy but this clearly represented a hopeful sign of improvement. The leg symptoms had also improved dramatically.



Post-operative lateral x-ray showing circumferential lumbar fusion using titanium cages with BMP anteriorly and pedicle screws connected by a PEEK (invisible on X-ray) rod.

She returned to physical therapy and began making slow and steady progress. Her incisional pain began to settle down. For the first time in over a year, she was able to sleep through the night. She began to taper down on her pain pills. Over the next six weeks, she continued to work with the therapists and began adding exercise to the stretching and core muscular strengthening.

When she returned for an office visit on January 15, 2009 she stated that she had absolutely no pain. She had no back pain, no lower extremity symptoms whatsoever and was very active. She completed a course of physical therapy, was back at work and doing everything that she wanted to do.

From the time of her initial evaluation in August 2008 to her most recent follow up visit in January 2009, only five months had past. She had undergone major reconstructive surgery to her lumbar spine and essentially was pain free and off all medications. She is our Spinetale given her outstanding dedication and commitment to getting herself better. The decision to undergo surgery seems easier when your life is colored by daily pain. Through the advances in spinal healthcare made possible through the work of The Spinal Research Foundation, the efforts of her physical therapists and the skill and expertise of her surgical team, Theresa is back where she wants to be. Theresa Scott is our Spine tale for the Spring 2009 journal because she is an amazing woman who was severely disabled by both back and leg pain and is now back to her usual life, just three months out from surgery. Clearly, innovations such as flexible rod technology and the use of recombinant human bone morphogenetic proteins have made an amazing difference in the healing course of these patients.

The Genetics of Spinal Disease

Marcus M. Martin, Ph.D. & Anne G. Copay, Ph.D.

Spine disease is one of the most common conditions affecting the developed world.[1] The two main factors which affect the incidence of spine disease are genetic predisposition and environmental influence.[2] Our physical traits are determined by our genetic makeup. Though the environment plays an important role in this equation, our genes, which contain our genetic blueprint, determine the base upon which environmental factors can act and our physiological response to them. As such, an individual's genetic makeup has a significant effect on the probability of developing spine disease. This review focuses on the influence of genetics on the development of spinal disorders. Several spine conditions have been identified as having a genetic basis. Such conditions include congenital scoliosis, congenital kyphosis/lordosis, ankylosing spondylitis, spondylolisthesis, degenerative disc disease, spinal stenosis, spinal tumors, osteoporosis, Padget's disease of bone, and osteomalacia.
Keywords: Intervertebral disc, Heritability, Gene, Spine

Spine Embryology

The spine is a complex structure. Its functions are to provide structural support to the body as a whole and a safe passage for the nerves and spinal cord. In the embryo, a precise cascade of events has to occur to result in the proper formation of the different elements of the spine. Alterations in the developmental steps can result in congenital abnormalities of the spine. Furthermore, other body systems in the embryo developing at the same time can be affected as well. Hence, congenital spine abnormalities are often associated with defects in the cardiopulmonary system and in the gastrointestinal and genitourinary tracts. For instance, up to 82% of patients with congenital scoliosis had associated malformations, most frequently of the genitourinary tract.[3]

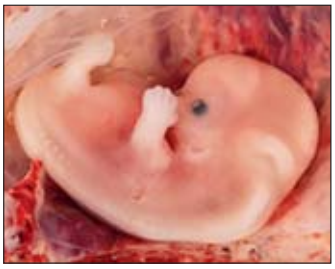


Figure 1. Developing spine in a 9-week embryo
(Picture courtesy of Ed Uthman, MD)

Congenital Spine Deformities

The incidence of congenital spine anomalies is estimated between 0.5 and 1 per 1000 births.[4] Congenital deformities of the spine are the result of anomalous vertebral development. Congenital malformations can be benign, in which case, they produce mild or no symptoms and may be visible only by radiological imagery. On the other hand, congenital malformations may be severe and produce marked spine deformity or other related conditions. The three major forms of congenital spinal deformity (kyphosis, lordosis, and scoliosis) refer to deviations from normal spinal alignment.[4]

Congenital Scoliosis is lateral spinal curvature resulting from anomalies of vertebral development. These anomalies are present from birth but may not be apparent until later in childhood after spinal growth increases their prominence.[5]

Currently there is a significant amount of research directed toward understanding the basis of scoliosis. There is strong evidence indicating that certain forms of scoliosis may be caused by abnormal genes.[5] These may affect the shape, intensity and direction of spinal curvature.

Epidemiological studies have shown the genetic basis of idiopathic scoliosis and suggest that there may be multiple modes of heritability of this condition.[5] There is currently a major research effort to identify the precise genes responsible for scoliotic phenotypes. Molecular studies have identified possible scoliosis related regions on chromosome 1,5,6,8,9,16,17,19 and X.[5] Clinical observation and population studies show a higher prevalence of scoliosis among the relatives of those affected by the disease compared to the general population.[6] Studies in monozygotic twins show 73% concordance made for idiopathic scoliosis.[6] Among dizygotic twins the concordance rate is 36%.[6] One study performed by Wyme-Dives and Risebourg showed that there may be an X-linked form of inherited scoliosis. Conflicting data as to the root of this disorder may implicate several genetic loci as causes of idiopathic scoliosis.

Congenital Kyphosis is a genetically inherited defect of the spine which can lead to severe abnormal kyphosis (hunch back). This condition is less common than congenital scoliosis. In some types of kyphosis, the spinal cord gets compressed, leading to paraplegia.[7]

The Genetics of Spinal Disease

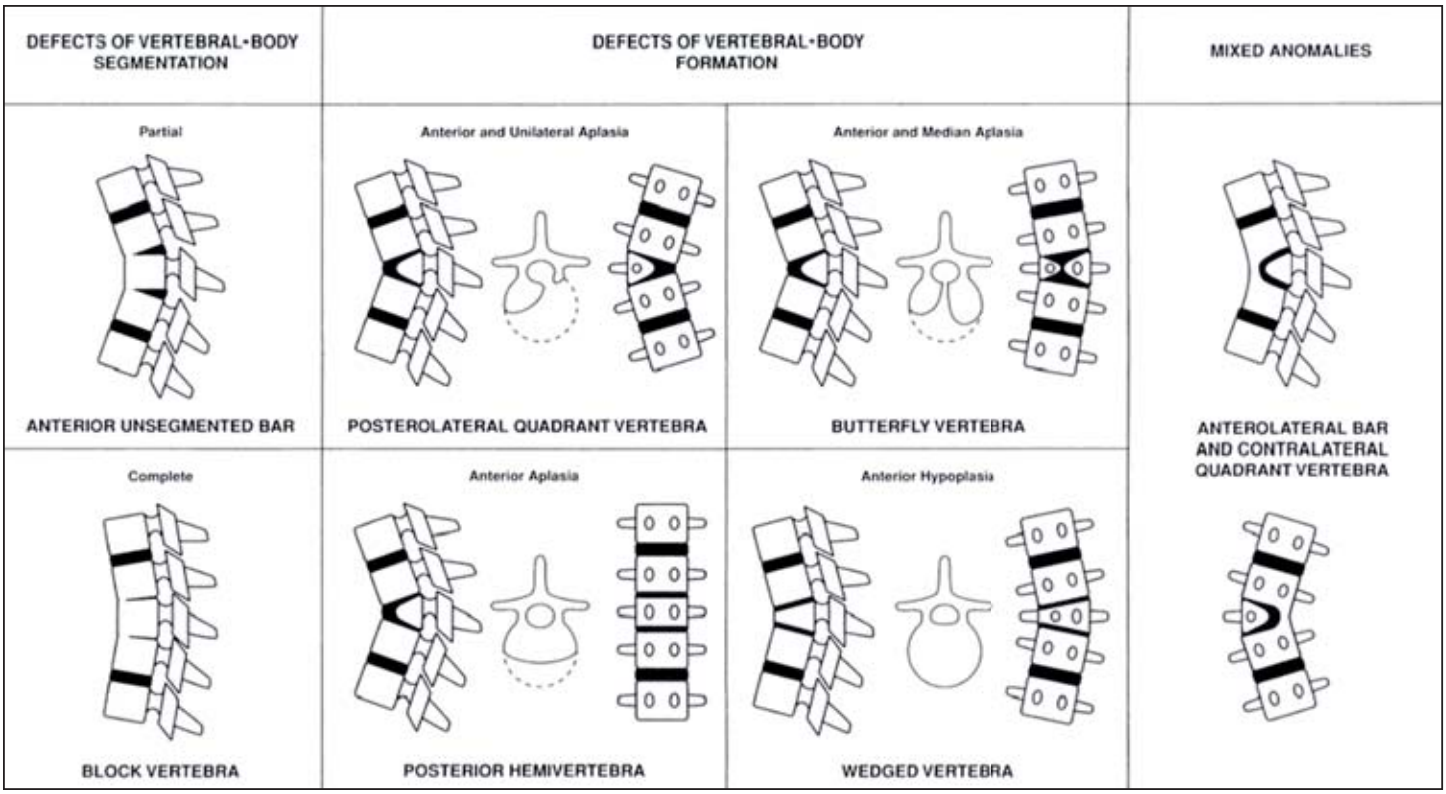


Figure 2. Drawings showing different types of vertebral anomalies
(reprinted from McMaster: J Bone Joint Surg Am, 1999, 81-A(10):1367-1383; with permission from Elsevier)

Congenital Lordosis is caused by the failure of posterior segmentation while anterior growth is active.[8] Congenital lordosis is rarer than either congenital scoliosis or congenital kyphosis. In the lumbar spine, this condition results in hyperlordosis where the spine begins to approach the anterior abdominal wall. When this condition occurs in the thoracic spine, the spine approaches the sternum and respiration is restricted.[8] Since this condition is usually progressive non-surgical approaches are typically not beneficial.

While congenital scoliosis rarely progresses to severe deformities, congenital lordosis and congenital kyphosis will typically do so.

The appropriate surgical procedure depends on the age of the patient, the type and size of deformities, and the possible spinal cord compression. In any cases, surgery should be done early before the deformities become severe. Surgery was better able to stop the progression and even achieve some correction of deformities in patients less than five years old.[7]

Spinal Stenosis is characterized by a narrowing of the spinal canal.[9] The cause of this condition may be either acquired or congenital (due to a genetic predisposition toward reduced spinal canal dimensions). Stenosis may cause the compression of the spinal cord and/or spinal nerves, possibly resulting in pain, loss of function and sensation.

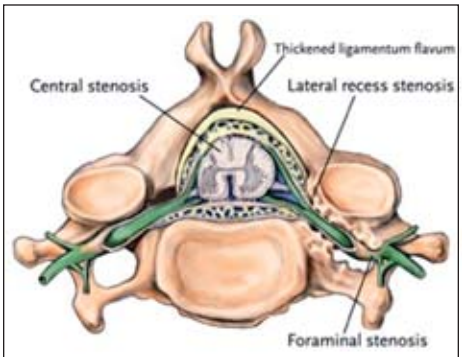


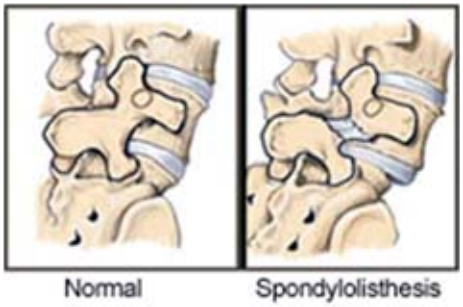
Figure 3. Spinal Stenosis
(Picture Courtesy Medtronic)

Spondylolisthesis is the anterior displacement of a vertebra or the vertebral column in relation to the vertebrae below. Depending on the amount of vertebral displacement, spondylolisthesis causes back pain, leg pain, and spinal deformity.

Genetics and the Spine

In the older population, degenerative disc disease commonly leads to spondylolisthesis. In younger patients, the most common cause of spondylolisthesis is a defect in the posterior part of the vertebra (a condition called spondylolysis). Spondylolysis is typically caused by stress fracture of the bone from athletic activities. Weight lifters, football linemen, and gymnasts have a higher incidence of slips than the general population.

Spondylolysis may be caused by a congenital defect in the posterior part of the vertebrae or a genetic susceptibility to stress fracture. There seems to be a strong hereditary factor associated with spondylolisthesis but no specific genetic anomaly has been identified so far.



Normal and spondolytic lumbar spines
(Picture Courtesy Medtronic)

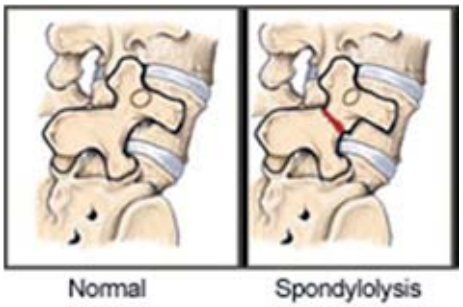


Figure 5. Normal and spondolytic lumbar spines
(Picture Courtesy Medtronic)

Meningomyelocele

The spinal arch forms a canal enclosing the spinal cord: the neural tube. Failure of the neural tube to close occurs during the first month of pregnancy (often before pregnancy is known). Failure of the neural tube to properly develop or close has effects ranging from unnoticeable to disastrous.

In Spina Bifida Occulta, the malformation is limited to the bony part of the neural tube. It is usually asymptomatic and occurs in 10 to 24% of the population. In Spina Bifida with meningomyelocele, the spinal cord protrudes outside the spinal canal. This can lead to paralysis, bladder and bowel incontinence, and be associated with severe forms of scoliosis, kyphosis, or lordosis. In a milder but less frequent form (Spina Bifida with meningocele), the spinal fluid and meninges protrude outside the spinal canal but not the spinal cord.

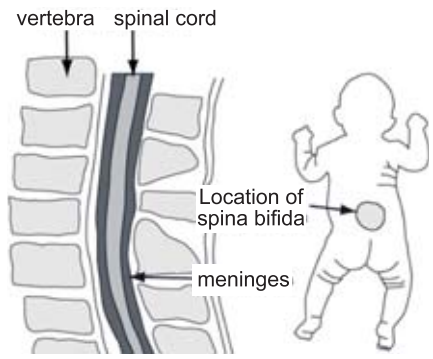


Figure 4. Spina bifida occulta
(Reprinted from the Center for Genetics Education: neural Tube Defects-Spina Bifida & Anencephaly, fact Sheet 59, www.genetics.edu.au, with permission)

Spina Bifida likely results from the interaction of multiple genes and environmental factors. A woman who has had one child with a neural tube defect, such as Spina Bifida, has about a 3% risk of having another child with a neural tube defect but can reduce that risk to about 1% by taking high doses of folic acid before and during pregnancy.

Osteoporosis

Osteoporosis is a skeletal disorder characterized by compromised bone strength (bone mineral density), predisposing patients to a higher rate of fracture.[10] This disease particularly affects the spine and family lineage studies show evidence of a genetic component. However, the specific genes which cause osteoporosis have not yet been identified.[11] Several candidate genes are being studied as possible cause of the development of osteoporosis (table 1). The etiology of osteoporosis is multifaceted. While many of the non genetic factors have been extensively studied, study of the genetic element of osteoporosis is relatively new. Control of this condition appears to be polygenetic and therefore identification of the responsible genes may take some time. This condition may be precipitated by mutations in structural or regulatory genes. Negative changes in bone mineral density may result from genetic variations in the vitamin D receptor gene expression, estrogen levels and collagen protein production. All these factors affect the strength of the vertebra and therefore the overall spine integrity.[10] However, further studies must be performed before the specific genetic elements responsible can be determined.

Low bone mineral density can often be an inherited trait but may not always correlate with the risk

The Genetics of Spinal Disease

of osteoporotic fracture.[11] In fact, fracture risk may have a genetic element independent of bone mineral density. In a study of post-menopausal women, wrist fractures were estimated to have about 25% heritability.[12] However, another study involving elderly twins failed to show evidence of heritability of fracture risk.[13] These divergent results may be due to a decrease in the importance of the heritability factor in fracture risk with age.

Paget's Disease of Bone

Paget's disease of bone (PDB) is a late-onset bone disorder which is characterized by focal areas of elevated bone turnover and the presence of highly enlarged hyperactive osteoclasts. In these areas, the bone formed is disorganized, weak, and prone to fracture. Many PDB patients are asymptomatic but some experience bone pain, skeletal deformity, pathological fractures, neurological symptoms, and deafness. PDB affected patients also show an increased susceptibility to osteosarcoma. The most commonly affected bones are the lumbar spine, sacrum, pelvis, femur, tibia, and skull. PDB may affect a single bone but more often affects several bones.

About 3% of Caucasian Americans above the age of 50 years age are afflicted with Paget's disease.[14] PDB diagnosis usually occurs after the fifth decade of life. However, its onset most likely starts during the third decade of life .[15] Paget's disease has a genetic basis and has been associated with mutations in the SQSTM1 gene region in about 40% of disease cases.[14, 15] The risk of developing PDB is about seven times greater in first-degree relatives of PDB affected individuals.[16]

Several rare inherited bone diseases show some overlap with classical PDB, i.e., increased bone turnover, bone deformity, and bone expansion. They differ from classical PBD in regard to onset time, affected bones, and severity of pathology.[17] Mutations in the TNFRSFI IA gene encoding RANK molecules are the cause of familial expansile osteolysis, early-onset familial PDB, and expansile skeletal hyperphosphatasia. Mutations in the TNFRSFI IB gene encoding OPG molecules are the cause of juvenile Paget's disease.[16] The early-onset forms tend to start in the second decade of life.[17] Juvenile Paget's disease or JPD presents in early childhood by increasing both bone formation and resorbtion.[18]

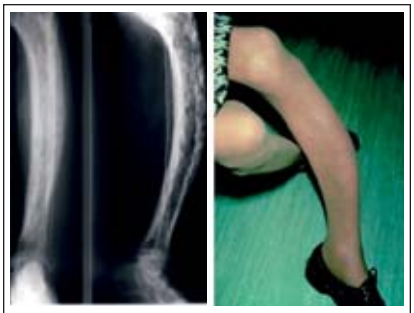


Figure 6. Extreme case of PBD of the tibia
(X-rays, courtesy of Ian Maddison)

Degenerative Disc Disease

There has been a major shift in the way scientists' view of disc degeneration over the last decade. Disc degeneration was previously believed to be mainly associated with occupation. However recent studies have indicated that genetics may play a stronger role than occupational factors in determining the state of spinal discs.[19] This research is providing us a more in-depth understanding of the etiology of degenerative disc disease and interactions between genes and the environmental conditions.[19]

Significant reduction in the disc space is a sign of disc degeneration. The narrowing of a single level is more likely to be the result of a traumatic event than the observation of systemic narrowing.[2,19] However, twin studies provide some of the most compelling evidence to support a genetic basis for some forms of disc degeneration.[2] In research performed at the University of Alberta, the spines of homozygous twins showed almost identical patterns of disc degeneration despite the differences in occupational spinal stress.[2] These results indicate that disc degeneration may be largely the result of genetic influences combined with some small measure of environmental effects.[20]

Figure 7. Vertebral fractures collapsed the spine
(Photos courtesy of the Bone & Joint Decade)

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a form of inflammatory arthritis which primarily causes inflammation at the inter-vertebral and sacroiliac joints.[21] It may

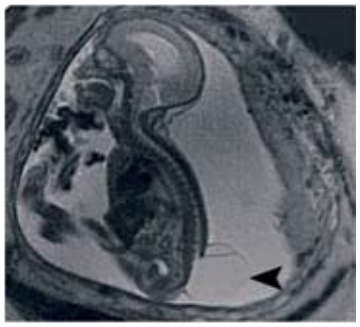


Figure 8. MRI of embryo showing myelomenongocele (arrowhead) and hydrocephalus
(Reprinted from Grimme & Castillio, Congenital Anomalies of the Spine, Neuroimag Clin N Am 17 (2007) 1–16, with permission from Elsevier)

also cause inflammation at the junction between tendons or ligaments and bone, between the ribs and spine, as well as eye complications.[22,23] This condition causes the formation of osteophytes and the fusion of the vertebrae. The prognosis is varied for this condition with some patients improving and some worsening. In some cases, disease progression is halted.

The specific cause of AS is unknown. However, the HLA B27 gene is believed to be associated with an increased rate of developing AS. There is a 2% chance that individuals with the gene will actually develop AS.[22] AS more commonly affects males than females and usually starts between the ages of 16-40. Some Native American tribes have a higher rate of incidence than in the general American population.[24]

Sacral Agenesis

Sacral agenesis refers to a group of conditions characterized by the absence of a variable portion of the caudal region of the spine. This congenital deformity occurs in 1 of 25,000 live births. This condition is associated with anorectal malformation, urogenital malformation and presacral masses. The exact cause of the disease is not known. The HLXB9 gene has been associated with an autosomal dominant form of this condition and has been used to identify asymptomatic heterozygotes.[25] Infants of diabetic mothers have 2 to 3 times the average incidence of congenital abnormalities and a 16% chance of developing sacral agenesis.[26]

Cervical Abnormalities

Some congenital abnormalities are specific to the cervical region of the spine. These abnormalities, though rare, are serious since they may result in severe neurological damage. Basilar impression, occipitocervical synostosis, and odontoid anomalies are the most common of the congenital malformations of the occipital junction and occur in about 2.5 of every 1000 live births. Early recognition may improve the chances of patients with these abnormalities.

Basilar Impression. This is characterized by a deformity of the bones at the margin of the foramen magnum at the base of the skull. This condition causes the floor of the skull to be indented by the upper cervical spine and the odontoid tip to protrude higher into the skull. This could lead to neurologic damage, injury to the annulus, and discharge of the cerebrospinal fluid. Two levels of those conditions are: primary and secondary. Primary basilar impression is associated with some other abnormalities. Secondary basilar impression is caused by softening of the bone and the deformity usually shows up later in life.

Occipitocervical Synostosis. This condition is a congenital malformation resulting in a part or complete union between the atlas (C1) and the base of the occiput of the skull. This condition is also called occipitalisation of the atlas.

Gene	Function
Vitamin D receptor	Critical in the regulation of BMD
Collagen type I aI	Encodes the aI chain of type I collagen
Estrogen receptor a	Estrogen receptor a encoded by ESR1 gene
Transforming growth factor b1	Encodes some growth factors associated with BMD and/or osteoporotic fractures
Lipoprotein receptor-related protein 5	Mutations of this gene cause a rare recessive osteoporosis pseudoglioma syndrome
Sclerostin	Mutations cause Van Buchem disease and sclerosteosis
TCIRG1	Mutations of this gene cause a small subgroup of patients to develop recessive osteoporosis
CLCN7	Encodes chloride channels that are important to osteoclast function.

Table 1. Genes under investigation

The Genetics of Spinal Disease

Odontoid Anomalies. Odontoid anomalies occur at the odontoid process and may involve complete absence (aplasia) of the odontoid process to partial absence (hypoplasia) of the dens from the axis (odontoideum). This anomaly may result in atlantoxial instability, neurologic defect or even death. The frequency of this anomaly is undocumented.

Other Disease Syndromes Associated with Congenital Spinal Deformity

Down Syndrome. This syndrome is characterized by flat faces, hypotonia, small ears and slanted palpebral fissures. About 37% of individuals with Down Syndrome have incomplete fusion of the lower spinal vertebral arches; 12% have atlantoaxial instability; 6% have abnormal odontoid processes, and 26% have hypoplastic posterior C1 arches. Many patients develop symptoms while under the age of 10.

Chromosome number 5 Syndrome. This condition was first described by Lejeune in 1963. The condition is associated with scoliosis, hemivertebrae, cat like cries in infancy, downward slanting palpebral fissures, and microcephaly.

Kabuki Syndrome. Kabuki syndrome was first described by Kobilinsky in 1883. This syndrome is associated with skeletal deformity such as scoliosis, hip dislocation, unusual finger length, rib abnormalities, brachydactyly and sagittal cleft of the vertebral bodies.

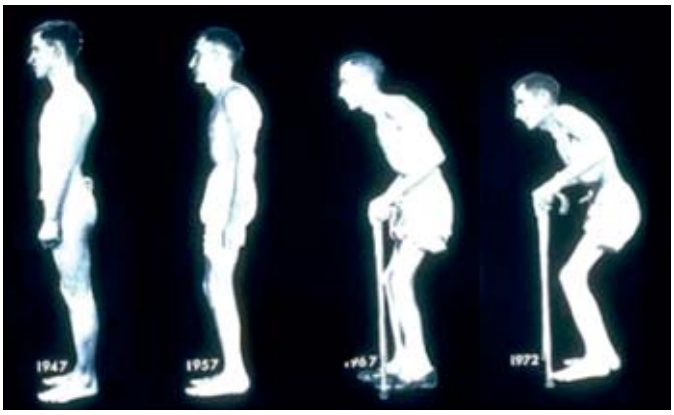


Figure 9. Debilitating effects of Ankylosing Spondylitis
(From Little et al. (1976): Upward subluxation of the axis in ankylosing spondylitis. A clinical pathologic report The American Journal of Medicine 60 (2):279-285, with permission from Elsevier)

Aarskog Syndrome. Aarskog Syndrome was first characterized by Aarskog in 1970. This condition is associated with skeletal abnormalities, scoliosis, metatarsus adductus, cubitus valgus, broad thumbs and great toes.

Cervico-oculo-acoustic Syndrome. This condition was first described by Wildervanck in 1952. It is associated with fusion of 2 or more cervical (sometimes thoracic) vertebrae, Sprengel deformity, torticollis, and abducens paralysis.

MURCS Association. This was first described by Duncan in 1979. This condition is associated with cervicothoracic vertebral defects in about 80% of these cases, most often between C5 and T1. There are often rib abnormalities, upper limb defects and Sprengel deformity.

VACTERL Syndrome. This disorder is associated with vertebral defects in about 70% of cases, limb bud anomalies, cardiac anomalies, anal atresia, and tracheoesophageal fistula.

Jarcho-Levin Syndrome. This condition was identified by Jarco and Levin in 1938. The disease patterrn has autosomal recessive. However, there have been reports of autosomal dominant inheritance. This condition is associated with multiple rib and vertebral abnormalities, posterior fusion, absence of ribs. Kyphoscoliosis, lordosis, crab-like rib cage and short trunk dwarfism.

Proteus Syndrome. Proteus Syndrome has been associated with sclerosis, kyphosis, hip dislocation, dysplastic vertebrae, knee and skull defects and abnormal bony prominences.

Other Syndromes associated with congenital spine disease include multiple synostosis syndrome, Coffin-Lawry syndrome, spondylo-carpo-tarsal synostosis, Gorlin syndrome, arteriohepatic dysplasia, fibrodysplasia ossificans progressiva syndrome and Morquio syndrome.

Conclusion

Spine disease represents a major medical and social burden to modern society. Current scientific endeavor has greatly increased our understanding of

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these conditions. It is now widely recognized that genetic predisposition has a significant effect on the probability of development of spine disease. This research has been reinforced by epidemiological and familial studies which indicate a genetic basis for several spine diseases such as congenital kyphosis, scoliosis, lordosis, and disc degeneration. Many congenital deformities of the spine are benign. However, several of these conditions can result in debilitating spinal deformity. Spinal abnormalities are also associated with several congenital syndromes. These often have an effect on multiple physiological systems. The identification of the genes responsible for these conditions is a difficult prospect but may lead to the developments of novel treatments (such as gene therapy) and new technology (such as genetic testing to allow for the detection of the condition even before it causes obvious deformity). This knowledge would also inform parents of the probability of their offspring developing spine abnormalities.

Genetics and environment both influence the incidence of spine disease. It was previously thought that environmental factors were the key variables in determining the development of spine disease. However, current research shows that one's genetic make-up appears to be the main factor in determining if a person will or will not develop spine disease.

Marcus M. Martin, Ph.D.

Dr. Martin's research interests include virology, immunology and neuroimmunology. He is engaged in collaborative research through SRF, with the Medical University of South Carolina Children's Hospital, geared toward the development of neuroprotective and neuroregenerative compounds for the treatment of nerve pathology.

Anne G. Copay, Ph.D.

Dr. Copay studies the outcomes of surgical and non-surgical spine treatments. She published several articles on the outcomes of spine fusion. She has ongoing research projects concerning the effectiveness of new spine technologies and the long-term outcomes of surgical treatments.

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The Genetic Basis of Adolescent Idiopathic Scoliosis

Christopher R. Good, M.D.

Scoliosis is an abnormal curvature of the spine that affects approximately seven million people in the United States. Adolescent idiopathic scoliosis is most commonly diagnosed between the ages of 10 to 12 years old and may be discovered by parents, during school screenings, or at pediatric visits. When scoliosis is suspected, patients are referred to orthopedic scoliosis specialists who evaluate the patient to determine the severity of the patient's curvature.

Treatment options for idiopathic scoliosis include observation, bracing, and surgery. In general bracing is recommended for curves between 25-30 degrees in patients with significant growth remaining and corrective surgery is generally reserved for progressive scoliosis curves greater than 45° or curves that do not respond to bracing treatment. The goals of scoliosis correction surgery are to correct the spinal curvature and to prevent the curve from progressing further during the patient's life.

The involvement of genetic factors in the development of adolescent idiopathic scoliosis has become widely accepted. At present, the general consensus is that the etiology of idiopathic scoliosis is multi-factorial. Exciting new research has recently been presented regarding the use of genetic testing to predict curve progression and failure of brace treatment in patients with adolescent idiopathic scoliosis. *Keywords:* Adolescent Idiopathic Scoliosis, Genes, Genetics

Adolescent Idiopathic Scoliosis (AIS)

Scoliosis is an abnormal curvature of the spine that affects approximately seven million people in the United States. Idiopathic scoliosis is a well characterized condition in humans. Abnormal curvatures of the spine were first recognized by Hypocrites and the name idiopathic scoliosis was introduced in the mid 1900s by Bower[1]. Idiopathic scoliosis is a structural curvature of the spine with lateral and rotatory components which typically affects 2 to 3% of normal children in adolescence. Severe, progressive curves are rare, and occur in only 0.2 to 0.5% of patients with adolescent idiopathic scoliosis.

Adolescent idiopathic scoliosis is most commonly diagnosed between the ages of 10 to 12 years old. It may be discovered by parents, during school screenings, or at pediatric visits. When scoliosis is suspected, patients are referred to orthopedic scoliosis specialists who will evaluate the patient to determine the severity of the patient's curvature.

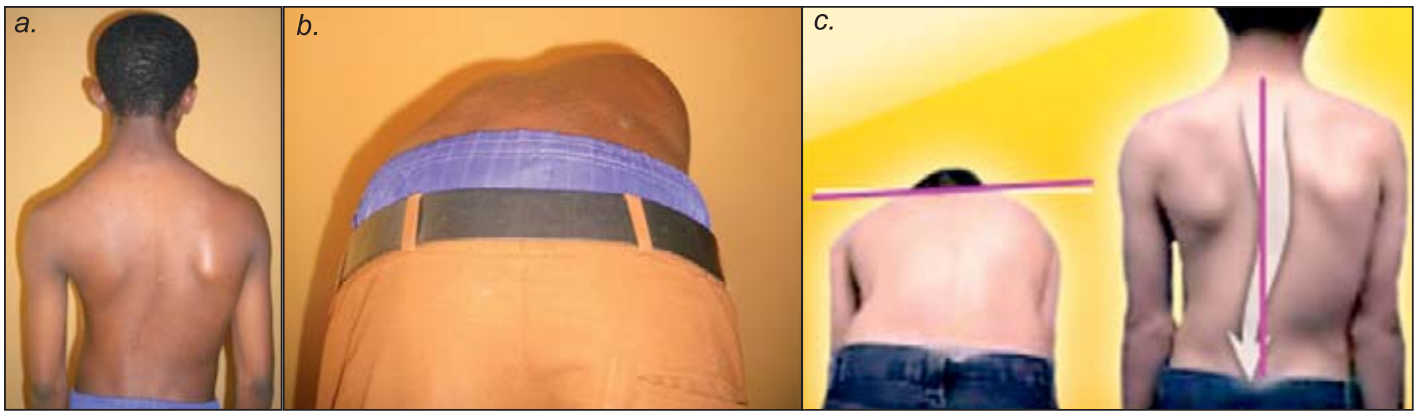

Figure 1. A scoliosis examination is done with the patient standing in a relaxed position with their arms at the side. The physician examines the patient from behind looking for curvature of the spine, shoulder blade asymmetry, waistline asymmetry or any trunk shift. The patient is then asked to bend forward at the waist and the physician examines the back once again to look for the rotational aspect of the scoliosis in the ribs or waist. (Figure 1c: courtesy Medtronic)

Genetics and the Spine

Scoliosis is typically characterized by a three-dimensional deformity of the spine that involves a curvature in the sagittal, frontal, and transverse plane (Figure 1). Adolescent idiopathic scoliosis does not typically produce significant morbidity for the patient; however, larger scoliotic curves or curves with significant rotation may cause a bothersome cosmetic deformity. In addition, large scoliotic curves may decrease pulmonary function and in the most severe cases can lead to a type of heart failure known as cor pulmonale.[2]

Different factors seem to be related to the risk for curve progression in adolescent idiopathic scoliosis. Specific factors include the age of the patient at the time of diagnosis, the maturity of the patient as determined by menarchal status and Risser sign, and the pattern of the scoliosis curve that is present. In this type of scoliosis, girls are eight times more likely than boys to have curves that progress to a point that treatment is ultimately required.[3-6]

Treatment options for idiopathic scoliosis include observation, bracing, and surgery. Mild cases of scoliosis are carefully observed with periodic physical examination and x-ray screenings (Figure 2). Most patients are seen on a 4 to 6 month basis until they finish growing and the majority of patients who are observed will have small curves that will have little if any progression as the patient reaches the end of growth. For patients with small curves who are observed, full activities are allowed including competitive sports.

Patients with curves that are at risk for progression during periods of rapid growth may need to be treated with a brace. In general bracing is recommended for curves between 25-30 degrees in patients with significant growth remaining. In most cases, a low profile brace known as a thoracolumbarsacral orthosis (TLSO) is recommended (Figure 3). A number of different bracing schedules have been described, but at present, I recommend a 22-hour-per-day bracing program. This maximizes the positive effects of wearing the brace while still allowing the patients time out of the brace for social activities and sports. Brace treatment is usually continued until the patient completes their growth, which means that teenagers who are treated with a brace will usually wear the brace between 2-3 years.

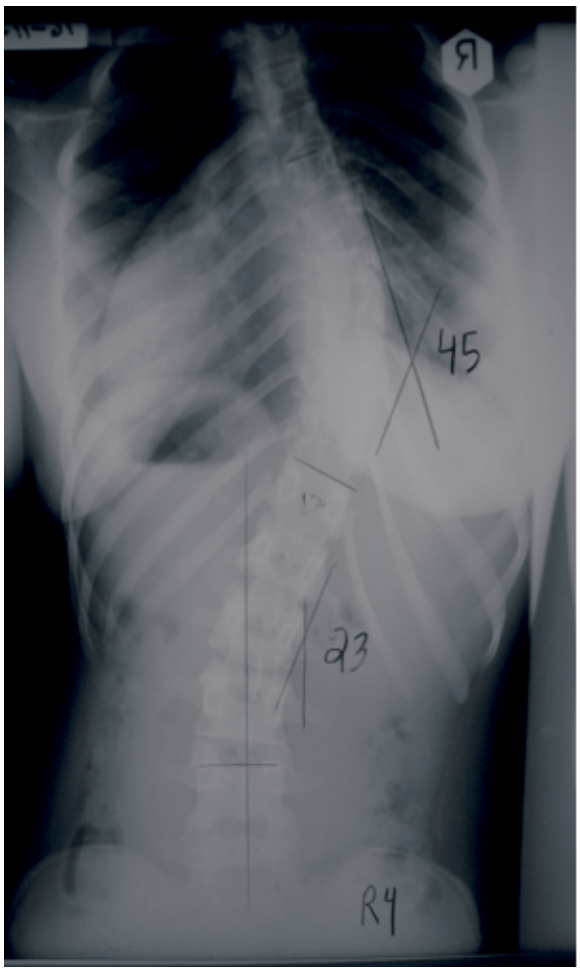

Figure 2. Full length spine x-ray of a patient with idiopathic scoliosis

Spinal reconstructive surgery is generally reserved for progressive scoliosis curves greater than 45º or curves that do not respond to bracing treatment. The goals of scoliosis correction surgery are to correct the spinal curvature and to prevent the curve from progressing further during the patient's life (Figure 4). A number of recent technical advances have taken place which allow for greater curve correction, and earlier spinal stability. Because of these advances, most patients undergoing reconstructive surgery for adolescent idiopathic scoliosis are no longer required to wear a brace after surgery and typical hospital stays after surgery are less than one week. The decision to undergo surgery for scoliosis should only be made after a very careful evaluation and a detailed discussion between the patient, family and surgeon.

The Genetic Basis of Adolescent Idiopathic Scoliosis

Biomechanical pathogenesis of AIS

Idiopathic scoliosis is a common pediatric spinal deformity and up to 80% of cases occur in adolescents.[7] Recent research has worked to identify potential factors involved in the etiology of scoliosis in order to enable physicians to more accurately predict the prognosis for patients with scoliosis and to offer more effective treatments. Although the exact etiology of adolescent idiopathic scoliosis is still unknown, a number of studies have examined a variety of neurologic, and skeletal factors that may be involved in the development of scoliosis.

Figure 3. A thoracolumbarsacral orthosis (TLSO) is sometimes used to treat scoliosis in patients who are still growing.
(Picture courtesy Medtronic)

Idiopathic scoliosis is unique in that it occurs exclusively in humans.[8,9] When scoliosis is seen in other vertebrates, it is either congenital, cicatricial, neuromuscular, or experimentally induced.[10] It is well established that humans are the only vertebrate animals that regularly stand with a fully erect posture. It has been postulated that this fully erect posture may be involved in the development of idiopathic scoliosis.[11-13] In addition, human beings are the only animals that walk with the body's center of gravity located directly above the pelvis. Other animals closely related to humans in the ape family, walk leaning forward with the body's center of gravity well in front of the pelvis.[14] The fully erect posture of the human spine significantly changes the conditions under which forces are transmitted through the spine and these unique forces may play a role in the development of idiopathic scoliosis.[15]

Genetics of Adolescent Idiopathic Scoliosis

The involvement of genetic factors in the development of adolescent idiopathic scoliosis has become widely accepted. It is possible that genetic factors may be involved in specific aspects of scoliosis including the shape of a scoliosis curve and the risk for curve progression. A number of population studies have documented that scoliosis runs within families and that there is a higher prevalence of scoliosis among relatives of patients with scoliosis then within the general population.[16]

A number of studies have examined the role that hereditary or genetic factors may play in the development of idiopathic scoliosis. In 1968, Wynne-Davies conducted a screening study of 114 patients with idiopathic scoliosis. They screened first, second, and third-degree relatives of patients with idiopathic scoliosis. Based upon inheritance patterns amongst these patients and their families, the authors concluded that a dominant or a multiple-gene inheritance pattern was present in adolescent idiopathic scoliosis[17]. In another study, Robin and Cohen carefully evaluated the inheritance pattern of adolescent idiopathic scoliosis over five generations within one family. They found the direct transmission of adolescent idiopathic scoliosis from father to son on more than one occasion, which does suggest an either autosomal or multiple-gene inheritance pattern.[18]

Large population studies have shown that 11% of first-degree relatives of patients with scoliosis have scoliosis. Similarly, 2.4% of second-degree and 1.4% of third-degree relatives of patients with scoliosis have the condition. Studies on identical and fraternal twins have shown that monozygous (identical) twins have a high concordance rate for the condition at approximately 73%, while dizygous (fraternal) twins have a concordance rate of 36%.[19-23] The incidence of scoliosis amongst dizygous twins is similar to that of first-degree relatives of a patient with adolescent idiopathic scoliosis.

At this time, the specific genes that are involved in adolescent idiopathic scoliosis have not been completely identified. Recent studies using a technique called genetic linkage analysis have identified multiple specific regions on a number of genes that may be involved with the development adolescent idiopathic scoliosis.[24-27] In 2005, Miller et al. performed a statistical linkage analysis and genetic screening of 202 families with idiopathic scoliosis. Using linkage analysis they were able to identify candidate regions for idiopathic scoliosis on chromosomes 6, 9, 16, and 17.[28]

The Difficulty of Studying the Genetic Basis of Idiopathic Scoliosis

Studying the genetics of adolescent idiopathic scoliosis is difficult because there is a high degree of genetic variability amongst patients with scoliosis.[29] For AIS, it is likely that a number of different genetic and environmental factors are involved in the development of scoliosis in any given patient. Even when a single gene is responsible for the development of a condition, not all patients with the gene may demonstrate the exact same characteristics. It has been well established that the patterns of inheritance of a single gene are susceptible to the principles of variable penetrance and heterogenicity. The principle of variable inheritance states that two patients with the same gene do not necessarily have to have the exact same characteristics. The principle of heterogenicity refers to the potential presence of many different genetic defects, all of which may eventually cause the same disease. This may be due to multiple different mutations of the same gene or multiple different genes that may all eventually lead to the same disease state. Because of the principles of variable penetrance and genetic heterogenicity, a simple mode of genetic inheritance may not always be clearly identifiable in one group even when a genetic basis clearly exists.

Figure 4. Postoperative x-ray of a patient with adolescent idiopathic scoliosis

At present, the general consensus is that the etiology of idiopathic scoliosis is multi-factorial. Continued research in the field will hopefully lead to the identification of specific factors that may cause the disorder. In the future, it is likely that genetic testing will lead to earlier diagnosis and treatment of the condition.

Genetic Testing for AIS

Exciting new research has recently been presented regarding the use of genetic testing to predict curve progression and failure of brace treatment in patients with adolescent idiopathic scoliosis. Kenneth Ward, MD and colleagues presented their preliminary work on genetic testing for AIS curve progression at the 2008 Annual Meeting of the Scoliosis Research Society. They reported the reports of a Genome-wide association study using Affymetrix HuSNP 6.0 microarrays to compare patients with idiopathic scoliosis with normal patients. The authors were able to identify genetic markers which were associated with progression of a scoliosis curvature. By using this panel of genetic markers, physicians may be able to predict which patients are likely to progress to a severe scoliosis at the time they are initially diagnosed.[30]

Also at the 2008 Annual Scoliosis Research Society Meeting, James Ogilvie, MD and coauthors also presented their work using genetic testing to predict which patients will not have successful brace treatment for AIS. The study tested prognostic genetic markers for brace-resistant adolescent idiopathic scoliosis in fifty-seven patients with adolescent idiopathic scoliosis who wore a brace for at least one year but had curves that progressed and required surgery. By using a panel of genetic markers, the authors were able to predict which patients were likely to fail brace therapy.[31]

The Genetic Basis of Adolescent Idiopathic Scoliosis

A New Genetic Test for Adolescent Idiopathic Scoliosis

A company named Axial Biotech has recently announced the release of a new DNA test that will soon be released to indicate the likelihood of progression to a severe curve for children with adolescent idiopathic scoliosis.[32] The test will be used for patients with mild or moderate adolescent idiopathic scoliosis between the ages of nine to thirteen years old. The simple test is performed analyzing the patient's saliva, which can be collected during a routine office visit. The test will allow scoliosis specialists to better predict an individual's risk for developing progressive scoliosis. Genetic testing will allow the physician to offer earlier and safer treatment to patients with high risk for spinal curvature, before the scoliosis progresses to the point that it causes severe pain or requires a major surgical reconstruction. In the future, it is likely that smaller surgical procedures will be available to straighten a small curvature that was detected through genetic screening.

Conclusion

Many factors may be related to the development of idiopathic scoliosis and no single cause has been identified at this time. Adolescent idiopathic scoliosis appears to be highly dependent on genetics as well as to the unique biomechanics of the human spine. A number of recent breakthroughs in genetic testing will lead to improved diagnosis and treatments for patients with adolescent idiopathic scoliosis.

Christopher R. Good, M.D.

Dr. Good has extensive training and experience in the treatment of complex spinal disorders with special expertise in non-operative and surgical treatment of adult and pediatric spinal deformities including scoliosis, kyphosis, flatback, and spondylolisthesis. Dr. Good has co-authored numerous articles and has been invited to lecture nationally and internationally at the Scoliosis Research Society, the International Meeting on Advanced Spinal Techniques, the American Academy of Orthopaedic Surgeons, and the North American Spine Society.

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Gene Therapy Approaches to Degenerative Disc Disease

Marcus M. Martin, Ph.D.

The development of novel approaches to the treatment of degenerative disc disease is a major challenge facing biomedical researchers. The current review highlights gene therapy methods and advances, as well as scientific evidence supporting a new approach to the treatment of degenerative disc disease in humans. Using gene targets such as BMP, TGFß, GDF5, SOX-9 and LIM-1 genes, researchers have had success in animal models. The intervertebral disc offers a unique environment for the application of these gene therapy approaches. Current research findings support the feasibility of this method of treatment. However, several safety concerns must first be addressed before this approach can be applied to the treatment of human intervertebral disc disease.
Keywords: Intervertebral disc degeneration, Gene therapy, Nucleus pulposus, Growth factor, Adenovirus

Back pain affects up to 85% of Americans at some point in their lifetime and is the second most common cause of physician visits in North America.[1] Of these, the most common cause of chronic back pain is associated with inter-vertebral disc degeneration.[1] Degenerative disc disease (DDD) involves the deterioration of spinal discs causing loss of mass, reduced disc competency, change in biochemical properties and often results in nerve irritation and pain. Degenerative disc disease may result in several different clinical conditions, such as disc herniation, spinal stenosis, spinal instability, radiculopathy, and myelopathy.

Disc Structure

Inter-vertebral discs (IVDs) make up approximately one quarter of the spinal column and function as the shock absorbers of the spine.[2] The biochemical properties of IVDs directly affect their mechanical properties and strength. A healthy IVD is composed of two main layers, the outer annulus fibrosus, derived from embryonic notochord and mesenchymal cells, and the gel-like nucleus pulposus (NP) which is found at the center of the disc. The annulus is composed of several collagen sheets at different orientations displaying a crimping morphology. The result is a very strong tissue which is able to resist considerable hydrostatic stress forces. IVDs rely on diffusion for the movement of molecules in and out. IVD tissue only contains about 1% cells and is primarily composed of water, collagen, proteoglycans and other proteins. The most common proteoglycans present in the disc are chondrotin sulphate and keratin sulfate.[3] Collagen found in the vertebral disc is primarily type 1 and type 2 with a relative increase in type 1 collagen being indicative of disc degeneration.[4]

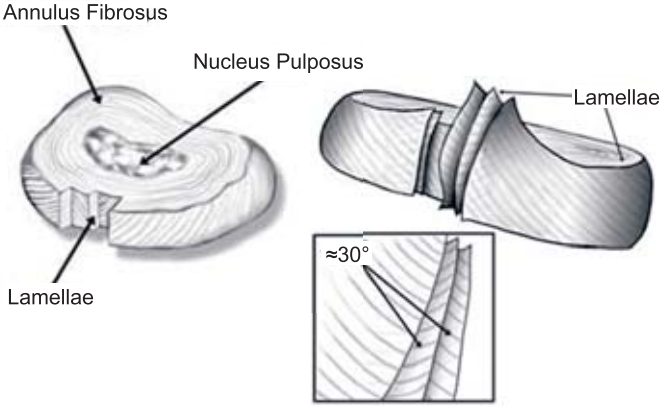

Figure 1. Intervertebral disc structure
(Picture courtesy of Medtronic)

Disc Degeneration

The properties of the IVDs change with time and are directly influenced by gene expression of the individual. The process of disc degeneration may involve genetic, mechanical and/or biologic factors. The early signs of disc degeneration have been noticed as early as the second decade of life.[5] Degeneration of the disc is a normal part of aging, but this process may become accelerated, resulting in the irritation of spinal nerves and causing pain. This is often accompanied by a significant reduction in the water content of the IVD. The nucleus contains more water than the annulus (70%- 80%).[6] Research performed at the University of Iowa illustrates that degenerated discs show reduced production of proteoglycans and proteins which are important to maintaining a healthy disc.[7] Therefore, one possible approach to the treatment of underlying degenerative disc disease may be to stimulate increased production of these molecules.

Gene Therapy Approaches to Degenerative Disc Disease

Disc degeneration is characterized by a change in the proteoglycan organization and concentration within the vertebral disc.[2] There is a decrease in the number and density of the cells and in synthetic activity accompanied by an increase in degenerative enzyme activity. Several factors have been associated with disc degeneration. One significant factor is age. By age 60, 90% of persons have at least one degenerated disc.[2] Other risk factors to inter-vertebral disc disease are genetic predisposition, tissue response to damage, decreased blood supply, occupational damage, and smoking. The most dramatic change in the biochemistry of degenerative discs is the reduction of water content, proteoglycan, and type II collagen in the nucleus pulposus.[8] This causes a reduction in disc height. Blood vessels may grow deeper into the disc from the outer annulus. Fissures and sclerosis of the surrounding bone may occur. Many inflammatory mediators have been identified in degenerative discs and these may play a role in the degenerative disc disease process. IL-6, TNF-a and maetalloproteinases (MMPs) have been associated with degenerative discs.[8] The natural inhibitors of MMPs are TIMPs. Using these genes and the genes of other degeneration associated molecule inhibitors as targets for up-regulation may offer an avenue to slow or stop inter-vertebral disc degeneration.

Current treatment options for disc degeneration include bedrest, anti-inflammatory drugs, discectomy and fusion procedures. These approaches, while they address end-stage manifestations of the disease, do not address the underlying conditions which precipitate them. As a result, even after treatment at one IVD level, other discs may degenerate to the point that they cause pain. What is urgently needed is a means by which one can halt or reverse disc degeneration. Gene therapy could possibly fill this niche. It presents the possibility of altering the biochemical environment within the IVD to strengthen its mechanical properties. This treatment could totally revolutionize DDD therapy.

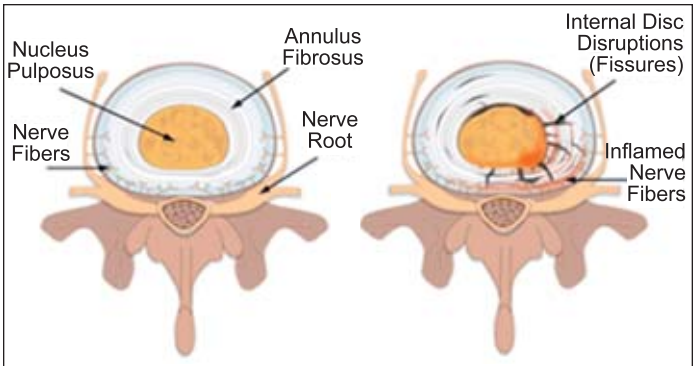

Figure 2. Normal intervertebral disc anatomy (Courtesy of Spinal Restoration)

Intervertebral disc with internal disc disruptions (Courtesy of Spinal Restoration)

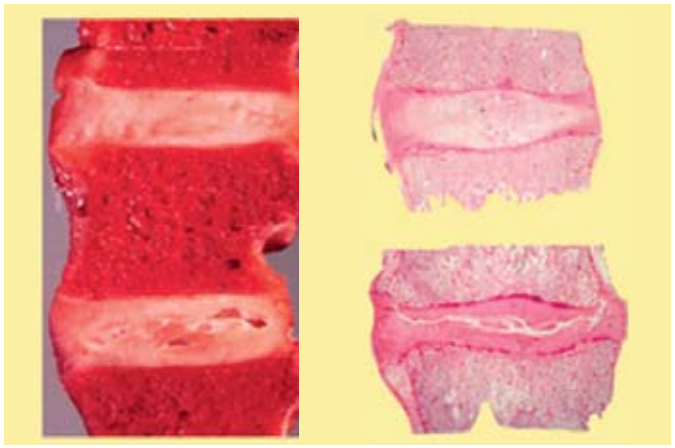

Figure 3. Healthy intervertebral discs (top) and degenerated discs (bottom). Reprinted from Saunders & Freemont, Chem. Sci., 2008,5,C45, with permission from the Royal Society of Chemistry

Gene Therapy

Gene therapy refers to the introduction of engineered genes into a live system geared toward achieving a therapeutic effect. One challenge of gene therapy has been to introduce a desired gene into an organism and have the gene or gene products affect specifically the target cells. Gene therapy of the IVD offers a unique environment for treatment: an anatomical area that is immune-privileged and non-vascularized. The cells of the inter-vertebral disc rely upon diffusion to obtain their needed molecules. This means that genetic material introduced into the disc space is more resistant to destruction, contained at the site and shielded from the host immune response. The use of gene therapy in this area could be performed through two main approaches: *ex vivo* gene therapy and *in vivo* gene therapy.

In an *ex vivo* gene therapy approach, cells are removed from the organism then transfected with the target gene. These cells are subsequently implanted at the intended site. The target genes are introduced into the cells by use of a viral vector, which is a virus modified to carry the genes into the target cells or by non-viral delivery systems.

Genetics and the Spine

Most *in vivo* techniques usually utilize viral vectors to carry the desired genes. These viruses are usually modified to prevent their infectivity. They are then introduced directly into the host to target the host cells. They facilitate the incorporation of the target gene into the host cell genome or extra nuclear localization depending upon the viral vector selected. When using an *in vivo* gene therapy approach, the target gene is introduced directly into the body. The delivery of the vector usually relies on diffusion to spread to the target cells. They are hampered by the minute intracellular spaces for transport. These are also restricted by viral binding ligands on the cell surface.

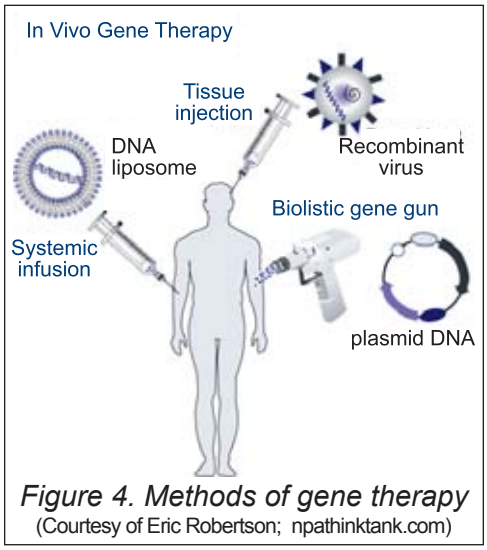

Figure 4. Methods of gene therapy
(Courtesy of Eric Robertson; npathinktank.com)

Viral Vector Gene Delivery Systems. Gene delivery systems are necessary in order to facilitate the uptake of the genes by target cells. Several types of systems are available to deliver genes into cells *in vivo*. These are divided into two main categories, viral vectors and non-viral vector systems. The viral vectors may be subcategorized as genome incorporating (including lentiviruses) and non-genome incorporating viral systems such as herpes and adenovirus vectors. The viruses of most clinical significance to gene therapy are adenoviruses, adeno-associated viruses and lentiviruses.

Adenovirus (AV). Adenovirus vectors are commonly used in gene therapy applications. One of the major advantages of this delivery system is its ability to infect non-dividing cells with high efficiency. This translates into a higher level of transient gene expression. The disadvantages of this system are the decrease in gene expression with time and the immunogenicity of adenovirus vectors which have been shown to cause joint space inflammation after injection. The immunogenicity disadvantage of this vector system may be circumvented if used in the immune-privileged environment of the IVD space. This may also facilitate gene expression for longer periods of time. However, because of the proximity of the disc to the spinal canal, an immunological reaction could cause potentially dangerous side effects.

Adeno-associated Viruses (AAV). Adeno-associated virus vectors appear to be less immunogenic than AV. Like AV, these viruses have high translation efficiency in both dividing and non dividing cells. This virus has not been linked to any disease in humans and inserts at a specific site on chromosome 19 without causing any major complications. The fact that they lack viral gene expression and have prolonged target gene expression make them a candidate for use in different tissue types. This vector can accommodate gene segments as large as most growth factors, making it an attractive target for gene therapy. After insertion of genes with AAV into cells, transgene expression could be observed up to 6 weeks after initial treatment, in studies performed *in vitro* on human cells and *in vivo* on rabbit NP cells.[9] Use of different variants of AAV show improved potency and a much broader cellular tropism.

Retroviral Vectors. Retroviruses provide a means of integrating genes into the chromosome of the target cells. The viruses are largely used for *ex vivo* gene transfer. These viral vectors also have some disadvantages. They are potentially oncogenic (cause cancer). Also, the introduction of genes at random points in the genome could silence the effects of essential genes. This approach to gene delivery presents major safety concerns and therefore is unlikely to be utilized in humans in its present form.

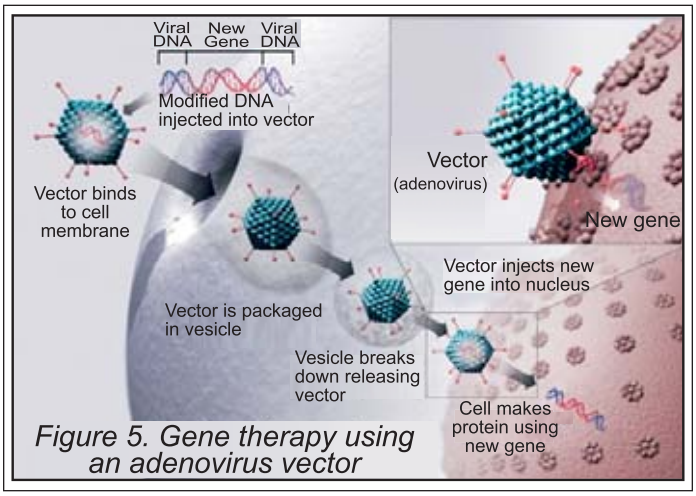

Figure 5. Gene therapy using an adenovirus vector

Gene Therapy Approaches to Degenerative Disc Disease

Non-Viral Delivery Systems. Non-viral delivery systems include gene guns, liposomes and calcium phosphate nano-particles conjugated with gene constructs. These methods facilitate the delivery of genes in an episomal manner but they may result in low transfection efficacy. Safety concerns with these approaches include contamination, vector safety, and toxic side effects.

Figure 6. A gene gun being used to transfer genetic material into cells in the lab
(Courtesy of Medical Research Council)

Potential Gene Targets

The balance between the breakdown and synthesis of the disc matrix proteins affects the overall mechanical properties of the disc. The goal of gene therapy treatment for disc disease is to tilt this balance to aid synthesis. Some strategies to accomplish this are growth factors, regulatory genes, and structural genes.

Structural Genes. These genes encode structural proteins which may be associated with disc degeneration. Structural genes are usually produced by a large number of cells in the disc space. Therefore in order to stimulate sufficient production of these molecules, a large number of cells may need to be transduced. Also, multiple structural gene targeting may be required to reverse disc degeneration. This may require the transfer of a significant amount of genetic material compared to just a one-target approach. Additionally, all structural proteins involved in disc degeneration have not yet been identified.

Regulatory genes. These include genes which encode molecules that affect cell metabolism within the IVD. These molecules may stimulate disc matrix production enhancement, transcriptional factors, cytokines and molecules which inhibit catabolism. Regulatory genes may cause the paracrine stimulation of nearby cells to produce multiple structural proteins. This could make it possible to use a smaller amount of material than if individual proteins were targeted. An ideal gene target would regulate several different cytokines with anabolic effects on the disc cells.

Growth factors. Several growth factors have been isolated from the inter-vertebral disc space. Some of these growth factors are BMP-2, BMP-4, insulin growth factor 1(IGF-1), beta fibroblast growth factor (ßFGF), platelet derived growth factors TGFß and growth differentiation factor. These may offer potential targets to stimulate disc regeneration.

Experimental evidence

The findings of Wehley et.al.[10] were one of the earliest illustrations of the utility of gene therapy in the treatment of IDD. In these experiments a retrovirus vector was utilized to transduce Lac-Z and IL-2 receptor antagonist genes into chondrocytes from bovine endplates. They proposed an *ex vivo* approach to gene therapy which involves removing endplate tissue, transducing these tissues with therapeutic genes, and then re-introducing them into the body. The transformed cells stimulated an improvement in the strength of the intervertebral disc.[10]

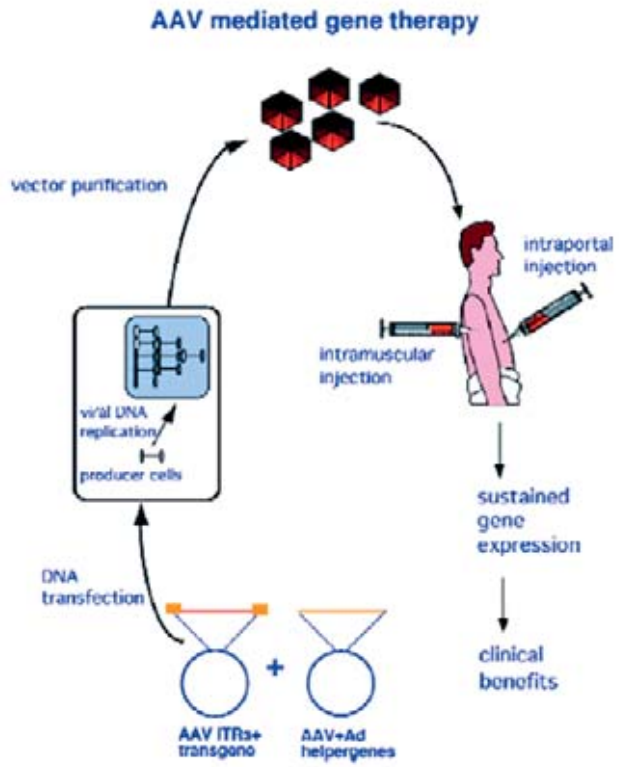

Fig 7. Reprinted from Nature Medicine 5, 21 - 22 (1999), "AAVant-garde gene therapy", R. Michael Linden & Savio L.C. Woo doi:10.1038/4698, with permission from Macmillan Publishers Ltd.

Even though the transduction rate was only 1%, this resulted in an increase in IL-2 receptor antagonist 48 hours later. In 1998, Nishida et al.[11] accomplished successful gene transfer in rabbit IVD models using AV vector transduction and transgene expression of the Lac-Z marker gene. They were able to detect gene expression up to 1 year after transduction. These findings support the feasibility of this approach. No adverse effects were reported during the study.

The results obtained using the marker proteins encouraged the application of this approach to deliver growth hormones. TGF-ß is a highly anabolic molecule which leads to a significant increase in proteoglycan synthesis in cells. In vivo studies using TGFß-1 in rabbit discs using a viral vector showed increased proteoglycan synthesis. Gene therapy of the IVD was accomplished in rabbits by Nishida et al.[11] using human TGF-ß1 and a viral vector. They noted a 30-fold increase in TGF-ß production in transduced discs. The proteoglycan synthesis increased 100% in the transduced group compared to untreated non-transduced discs. This study shows that gene therapy may be feasible for the treatment of inter-vertebral disc disease. Both studies showed no major immune response. This stimulated hope that approach might be applicable in humans.[12]

Experiments performed using cultured human nucleus pulposus cells showed encouraging results. Cells transduced with TGFß-1 showed increased protein expression and increased collagen and proteoglycan synthesis in the nucleus polposus up to 3 times the control group.

Encouraged by these findings, researchers then sought to apply this approach to anabolic and anticatabolic factors as gene therapy targets. Two other potential growth factor targets for use in gene therapy are bone morphogenetic proteins (BMPs) and IGF-1.

Bone morphogenetic proteins are a group of 20 proteins which have been identified as being related to embryogenesis and chondrogenesis. Currently BMP-2 and BMP-7 have been utilized for the enhancement of fusion rates after spinal fusion procedures. Current research shows that BMP-2 increases cell proliferation collagen type II synthesis, SOX-9 and TGFß-1 *in vitro*. This action causes a reversal in the matrix changes which characterize disc degeneration. Within *in vitro* studies using rabbit IVD, cells synthesized PG and collagen after exposure to BMP-7. It was also observed that cells in the early degenerative stages responded better to BMP-7 treatment.[13]

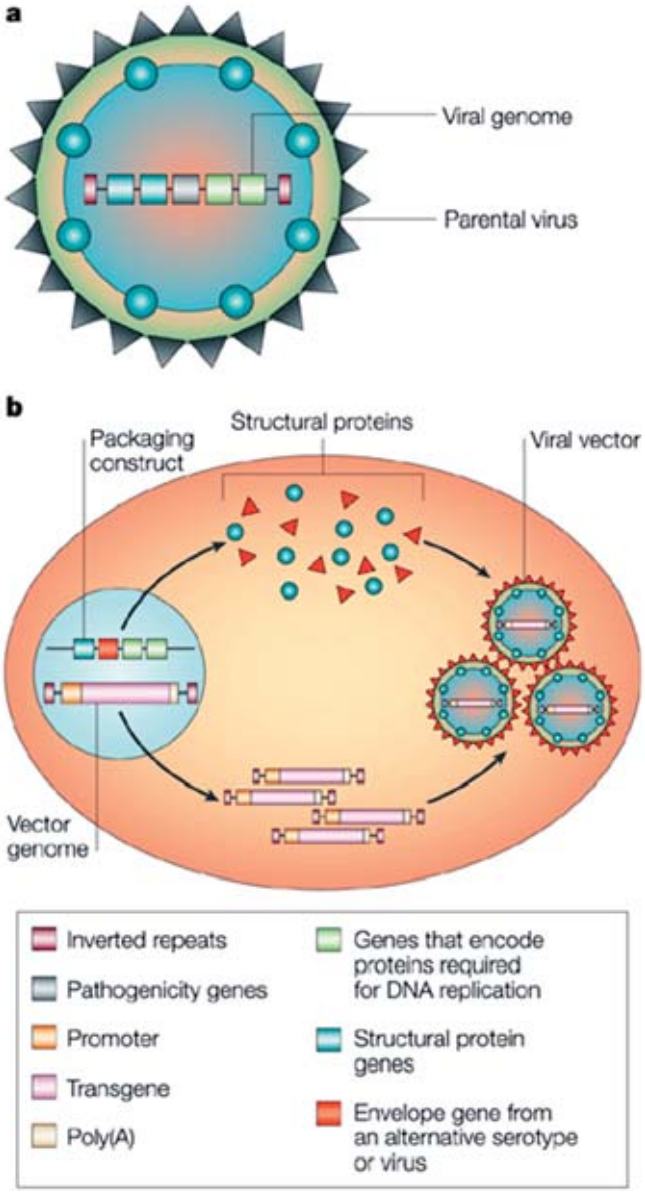

Figure 8. Converting a virus into a vector

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Gene Therapy Approaches to Degenerative Disc Disease

LIM mineralization protein is an intracellular protein which stimulates the secretion of several BMP molecules from osteoblasts including BMP-2 and BMP-7.[14] LMP-1 is a molecule that is associated with stimulating the production of several different BMP molecules. It appears to upregulate the production of BMP-2, -4, -6 and -7 when it is over-expressed in fibroblasts and leukocytes. Even with low doses of virus transduced with LMP-1, this gene therapy leads to the formation of bone both *in vivo* and *in vitro*.[14]

Anti-catabolic factors present another avenue to attempt arrest of disc degeneration. TIMP-1 is a natural inhibitor of MMPs which have been associated with disc degeneration. Gene transfer of TIMP *in vitro* into NP cells showed as much as a 5-fold increase in proteoglycan synthesis.[15] IGF-1 has also been observed to up-regulate proteoglycan synthesis in the disc cells.[15, 16.]

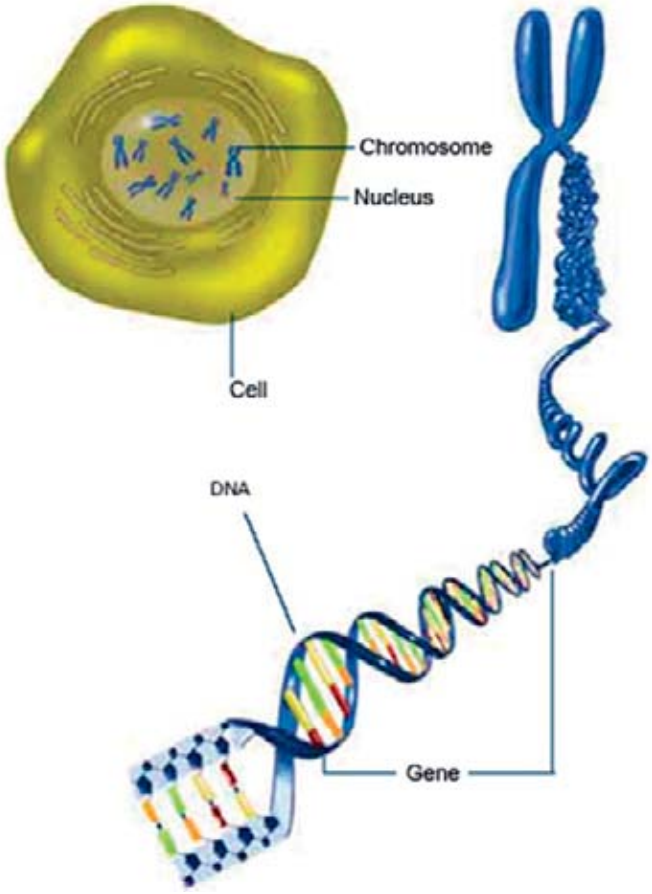

Figure 9. Diagram of the long, stringy DNA that makes up genes is spooled within chromosomes inside the nucleus of a cell
(Courtesy of The National Institute of General Medical Sciences).

The Sox-9 molecule is a cellular transcription factor which stimulates type II collagen synthesis and chondrogenesis. A 5 year in vitro study using the Sox-9 gene and an adenovirus vector demonstrated the ability of this protein to increase type 2 collagen synthesis and preservation of NP architecture.[17] Several other anabolic factors have shown promise in preliminary studies. GDF-5 deficiency has been associated with disc degeneration in mice. GDF-5 caused a restoration of disc height in rabbit disc degeneration studies.[18]

Recently, work done by Studer et al.[19] demonstrated that p38 MAPK inhibition in NP cells increases proteoglycan production suppressed by IL-1 and TNF-a. This indicates that the map kinase pathway may be important in the regulation of the anabolic/catabolic process within the vertebral disc.[19] Gene therapy has already shown potential in experimental treatment of DDD. Research done in animals has demonstrated the utility of the gene therapy approach.

Gene Therapy for Spine Fusion

Gene therapy might also be utilized in the enhancement of bone fusion in spine fusion surgeries. This approach would introduce genes which produce products that enhance bone formation and bone fusion. Some osteoinductive molecules are already being used to enhance the rate of bone healing. These include bone morphogenetic proteins. Gene therapy provides an opportunity to induce prolonged production of a target molecule at the target site. It facilitates addressing the problem of short periods of activation which occur when a protein is directly introduced at the target sites. If the genes coding for these proteins are introduced instead of the proteins themselves, there will be a higher chance of the gene product persisting at the site for a longer period. Potential target genes include BMP or LIM which have been shown to up regulate the production of BMP.

Challenges of Gene Therapy

Gene therapy also presents several major challenges, one of which is safety. Genes that do not integrate into the genome are less stable than those that incorporate into the genome. However,

vector systems which lead to gene incorporation into the genome may inadvertently silence other genes. Virus culturing may be necessary for generating sufficient material for therapeutic administration. The culturing of cells *ex vivo* may present the potential for infection of the target cells which may then be transferred to the recipient during treatment procedures. There may also be a challenge of low transduction frequency and insufficient expression of genes *in vitro*. Animal experiments have presented very positive findings. These may later facilitate the use of gene therapy in the treatment of human DDD. There is however, no ideal model system for DDD. Most involve the direct injury of the disc. These experiments are usually done using young animals, so their regenerative capacity may affect the experimental result.

Conclusion

There have been several significant breakthroughs in the development of gene therapy for the treatment of IVD. Gene therapy offers hope of providing treatment for several congenital conditions. Additionally, the contained, immune-privileged, and non-vascularized environment of the disc core may present the ideal conditions to utilize gene therapy. Several molecules represent potential targets. BMP, TGFß, GDF5, SOX-9 and LIM-1 all show promise in animal studies. Whether these approaches will also work in humans remains to be seen. However, before these approaches can be approved for human use, they must be shown to be both safe and efficacious. Since IVD is largely a non-lethal condition, the use of any form of intervention must be carefully considered. The gene therapy treatment approaches in the IVD would probably be implemented in the form of minimally invasive IVD injections. This presents a concern, since the target area is close to the spinal canal and nerve roots. Damage to these structures could result in debilitating and currently irreversible effects. Once the present safety concerns can be addressed, gene therapy promises to be a novel approach to treatment of disc degeneration. This approach would enable physicians to treat disc degeneration in a minimally invasive manner aimed at arresting the deterioration and facilitating the improvement of disc health.

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Physical Therapy as a Tool for Prevention of Common Pathologies

Michael W. McMurray PT, DPT, FAAOMPT

Physical therapists originally branched out of the nursing profession to assist people affected by polio. Originally known as restoration aides, these professionals dealt strictly with patients affected by polio and its effects. Their aim was to help patients regain as much mobility and function as possible. Since then, the profession has grown exponentially and, currently, physical therapists assist patients affected by a variety of problems ranging from ankle sprains to strokes.

Most people think of physical therapy exclusively as a treatment for pain or injury. However, over the last few years there has been a significant shift in the medical field toward prevention of disease or injury. Similarly, physical therapy has become involved in the prevention of injury and pathology. Numerous articles found that physical therapy was effective in improving balance, reducing falls, controlling type II diabetes, osteoporosis, osteoarthritis, and neck and low back pain. These common pathologies are partly due to genetics. Physical therapy may not be able to counter the genetic make-up but it definitely can help delay, minimize, and shorten the impact of these pathologies.

Balance and Falls

Balance deficits, and subsequent falls, account for a significant risk of injury in older adults. This topic has accounted for a significant amount of research in the literature over the last few years. A number of these studies have investigated the effects of a supervised exercise program on reducing falls and improving balance.[1-6] Various populations and interventions were investigated and all studies resulted in a significant balance improvement and reduction in falls. One study, in particular, investigated a community-based group exercise program developed by a physical therapist.[1] This exercise program lasted 12 months and involved participants over the age of 65. At the conclusion of this study, the rate of falls was 40% lower in the exercise program group than in the non-exercise program group. In this study, the interventions used included whole body muscle stretching, functional balance exercises such as sit to stand practice, reaching, weight shifting, dance steps, change of direction activities, stepping, and catching and throwing a ball.[1] Also included were strengthening exercises using body weight resistance as well as resistance bands and some type of aerobic activity.[1] An integral part of this program was the home exercise program that was given to the participants. An additional study by Lord et al. correlated the amount of compliance of the home exercise program to the frequency of falls following a similar 12-month exercise program.[6] In other words, the greater the compliance, the greater decrease in the frequency of falls.

Figure 1. Example of a balance exercise.

Figure 2. Healthy bone.
(Picture courtesy IOF)

Diabetes

Diabetes can be divided into 2 categories, type I and type II, or insulin dependent and non-insulin dependent, respectively. Persons with type I diabetes secrete no insulin while persons with type II diabetes secrete insulin but is not used effectively in the body. Exercise has not been found to be an effective means of controlling type I insulin dependent diabetes but has been found to be effective in helping to control type II, non-insulin dependent diabetes. Physical exercise causes increased insulin sensitivity and increased glucose metabolism. An effective exercise program for an individual diagnosed with type II diabetes should include aerobic activities as well as resistive exercise.[7] In a recent study by Ferrara et al., it was found that adding resistance training to an aerobic exercise program significantly increased the

subjects insulin sensitivity.[7] Physical therapists are specially trained in exercise prescription and are able to develop a safe and effective individual exercise program that incorporates aerobic and resistance exercise.

Osteoporosis

Osteoporosis and osteopenia are common musculoskeletal disorders that are characterized by a loss of bone density. Both conditions are influenced by an individual's genetic composition. In order to diagnose these disorders doctors will commonly use a bone density test.

Osteoporosis is classified by a t-score value of greater than –2.5, while osteopenia is classified by scores in the range of –1 to –2.5. Physical activity has been found to have a significant influence on reducing the effects of osteoporosis. As stress or force is placed on the bone (possibly through exercise), osteocytes are activated which will increase bone mass over time. Conversely, decreased load will result in decreased bone mass over time.[8] Research has shown that greater loads and lower repetitions result in greater gains in bone mass, however, any type and amount of loading and resistance has been found to be effective.[8] Physical activity, especially an exercise program involving weight bearing and resisted exercise, has been shown to be effective in preventing the onset of osteoporosis, as well as reversing the effects, if present.[9,10] Individuals diagnosed with osteoporosis must be cautious when beginning an exercise program. As the disease progresses, certain exercises and positions are contraindicated due to the risk of injury, or more specifically, fracture.[11] Physical therapists are specially trained in exercise prescription and will be able to develop an exercise program that is safe and effective in preventing or treating the effects of osteoporosis. In addition to strengthening, a physical therapist will also address other key topics associated with osteoporosis. These will most likely include posture, balance, strength, flexibility and nutrition.[11]

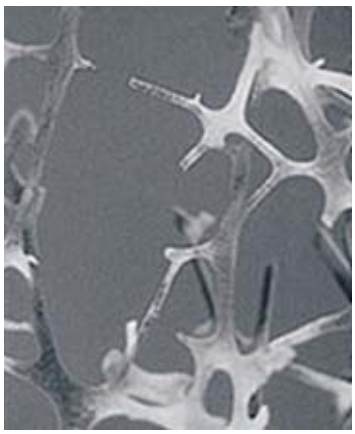

Figure 3. Osteoporitic bone.
(Picture courtesy IOF)

Osteoarthritis

Osteoarthritis is a prevalent musculoskeletal pathology that affects people from all walks of life and all ages. It is also considered the most common joint disease.[12] The causes of osteoarthritis are not known, although there is thought to be a genetic component as well as biomechanical influence.[12] What is known are the effects of osteoarthritis, ranging from loss of range of motion, loss of strength, loss of function, and pain. There are numerous research articles investigating the effect of physical therapy after the onset of osteoarthritis, but only a few could be found relating to the prevention of arthritis with physical therapy. Depending on the severity of the osteoarthritis, physical therapy has been shown to be an effective means of increasing strength, improving range of motion and improving function.[12,13] A physical therapist will use a variety of techniques and tools to accomplish these goals. The literature has shown that manual therapy techniques as well as a specific exercise program and a home exercise program are effective in the management of osteoarthritis.[14,15] In addition to these techniques, the physical therapist will most likely assess balance as well as gait and movement patterns.

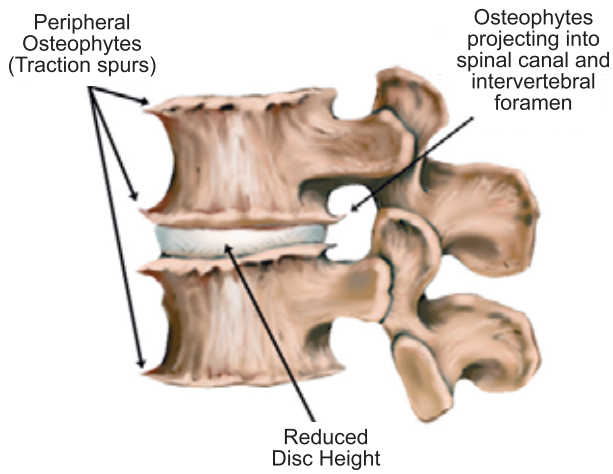

Figure 4. Osteoarthritis of the spine
(Picture courtesy Medtronic)

Physical Therapy as a Tool for Prevention of Common Pathologies

These factors can contribute to the onset and progression of osteoarthritis. The physical therapist will also prescribe a home exercise program which will be instrumental in maintaining range of motion, strength, balance as well as aerobic condition which may help to deter the onset of osteoarthritis.

Low Back Pain/Neck Pain

Low back pain and neck pain are two of the most prevalent causes of pain and disability.[16] There is a wide range of causes for neck and back pain including injury, poor posture, repetitive stress, genetics, improper ergonomics, muscle weakness, and injuries or pathologies to other areas of the body, to name a few. There have been significant amounts of research dedicated to the treatment and prevention of these disorders. In general, there are two types of prevention when discussing low back and neck pain: primary and secondary. Primary prevention is prevention prior to the onset of symptoms, while secondary prevention occurs after the acute onset of symptoms but prior to the onset of chronic symptoms.[16] The research dedicated to investigating primary prevention has had varying results.

Due to these inconsistent findings, the effectiveness of many of the current strategies for primary prevention could not be validated.[16] The research has had more success determining effective strategies for secondary prevention.[16] Theoretically, the strategies used after an acute episode would also be effective prior to the onset of symptoms, but this has not been proven in the literature thus far. The first of these strategies is core muscle training and strengthening. The core is made up of the transverse abdominus, multifidus and pelvic floor muscles. The transverse abdominus is the deepest abdominal muscle, which when contracted forms a corset around the trunk, which helps to stabilize the trunk during activity. The multifidus is a segmental spinal stabilizer which works along with the transverse abdominus and pelvic floor muscles to stabilize the spine during upright posture and activity. Likewise in the neck, the longus coli and capitus muscles serve to stabilize the neck during upright posture and activity. The literature has shown that after the onset of back or neck pain these muscles stop working effectively and begin to atrophy. In order to counteract this, a specific exercise program prescribed by a physical therapist will serve to restore the activation of these muscles so that they can stabilize the spine during activity. A whole body exercise program including aerobic exercise will also help to maintain strength, flexibility and muscle balance throughout the body. Performing these exercises will help the body maintain correct posture and prevent altered forces through the body, which eventually may lead to an acute onset of pain.[17, 18]

In addition to exercise and core training, proper ergonomics can serve as an effective means of preventing the onset or recurrence of neck or back pain.[19] An improper ergonomic set-up will result in poor posture, poor movement patterns and possible poor lifting mechanics. These will put undue stress through the body and eventually result in an acute pain episode. Contrary to popular belief, an ergonomic assessment encompasses more than the desk, chair and computer. A thorough ergonomic assessment will include evaluation of the entire workspace and how an individual moves in that space. This will determine how best to use the workspace so that there can be as little unwanted stress through the body as possible.

Conclusion

Physical therapy has been shown to be a safe, effective, and non-invasive means of prevention for a variety of pathologies including balance deficits, diabetes, osteoporosis, osteopenia, osteoarthritis, low back pain and neck pain. Physical therapists are highly trained health professionals who study movement, biomechanics, and exercise prescription. These professionals will utilize a variety of techniques including manual therapy techniques, exercise prescription, education and home exercise prescription in order to prevent the onset of these pathologies, or to decrease the risks associated with them. Utilizing these professionals for the prevention of common pathologies has been found to be beneficial in the research literature. While physical therapy may not be able to entirely prevent the onset of some of these pathologies, it may help to decrease the recovery time or severity of the onset.

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Michael McMurray has seven years of physical therapy experience with a diverse patient population ranging from the athlete to the geriatric patient, with varying diagnoses. He has undergone advanced fellowship training in orthopaedic manual physical therapy and is a Fellow of the American Academy of Orthopaedic Manual Physical Therapy.

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Congenital Defects of the Atlas: An Insidious Malformation

Dritan Pasku, M.D. & Pavlos Katonis, M.D.

The atlas is called the first cervical vertebra which supports the head. Anatomically, the atlas consists of two lateral masses connected by a short anterior and a longer posterior arch (Figure 1).

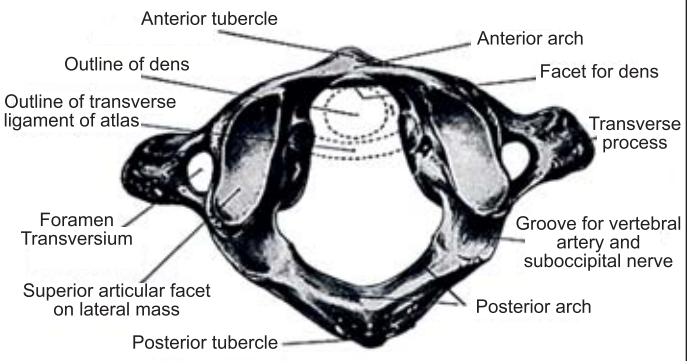

Figure 1. Anatomy of the atlas

Embryology

The embryology of the atlas is unique as it is the only vertebra to develop from only two lateral ossification centers, (one in each lateral mass), and a third ossification center for the anterior arch. The center in each lateral mass appears around the seventh week of fetal life. However, the anterior ossification center appears around the end of the first year after birth. The onset of ossification of the posterior arch of the atlas occurs during the seventh week of intrauterine life proceeding perichondrically from two centers located in the lateral masses. The lateral ossification nuclei fuse on midline posteriorly to give the posterior arch of the atlas.

Complete fusion of the posterior arch is expected to occur between 3 and 5 years of age. The anterior center usually fuses with the two lateral centers between 5 and 9 years of age.[1-4] A separate ossification center develops in the posterior cartilaginous cleft during the second year of life. This center is responsible for the complete fusion of the posterior arch of the atlas but a failure of chondrogenesis in this phase can lead to disturbed ossification. Observations performed at autopsies or intraoperatively show that connective tissue bridges the bony defects.[3-9]

Incidence and Classification

Malformations of atlas are relatively rare and exhibit a wide range including aplasia, hypoplasia and various arch clefts.[1,10] The reported incidence in a large study of 1,613 autopsies with regard to the presence of congenital aplasia is 4% for the posterior arch and 0.1% for the anterior arch (5-8). Recently, Senoglou et al. represented a frequency of 3.35% for the posterior arch and 0.01% for the anterior arch in 1,104 patients after a CT scan of the craniocervical junction.[2] In 1990, Villas et al. presented an anatomic classification of defects of the atlas and defined Area 1 as the posterior arch (Table 1).[11]

A complete classification of congenital anomalies of the posterior arch of the atlas was proposed by Currarino et al. based on seven of their own cases and 39 others and is described in the literature up to 1994 (Table 2).[12] The incidence of a type A anomaly is estimated about 97%, whereas only 0.69% of the general population has a type B-E anomaly.[12]

At least two anomalies can develop during the ossification process: 1) median clefts of the posterior arch and 2) varying degrees of posterior arch dysplasia.[2,13] A failure in ossification of the anterior part leads to rachischisis.[10]

Area1	Defect of formation of the posterior arch
Area2	Defect in union of posterior arch with superior articular facet
Area3	Defect of formation with hypoplasia or agenesis of superior articular facet
Area4	Defect of formation of the anterior arch
Area5	Malformation of atlanto-occipital junction
Area6	Malformation of atlanto-axial junction

Table 1.Classification of the congenital malformations of atlas according to Villas (1990)

Type A	Failure of posterior midline fusion with a small gap remaining
Type B	Unilateral clefts
Type C	Bilateral defects with preservation of the most dorsal part of the arch
Type D	Complete absence of the posterior arch with a persistent isolated tubercule
Type E	Complete absence of the entire posterior arch

Table 2. Classification of the congenital defects of posterior arch of atlas according to Currarino (1994)

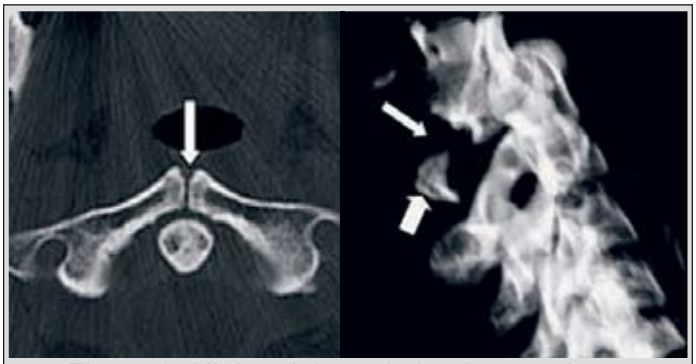

Figure 2. High axial resolution image shows the anterior rachischisis (arrow) and lateral 3D reconstruction shows to better advantage the complete atlas cleft (arrow) and the tubercle (thick short arrow).

Clinical Significance

Generally, patients are asymptomatic and are often discovered incidentally during radiological evaluation of neck trauma (Figure 2).[14]

Congenital absence or hypoplasia of the posterior arch of the atlas may be associated with several disorders, such as the Arnold-Chiari malformation, gonadal dysgenesis, Klippel-Feil, Down and Turner syndrome (Tab. 3).[2,4,13] On the other hand, it has been reported that hypoplasia of the posterior arch of the atlas may increase the risk of atlantoaxial subluxation in about 26% of children aged 2-3 years.[15] Currarino et al. reported an affected mother and son and Motateanu et al. reported an affected mother and daughter suggesting an autosomal dominant inheritance.[12,16] The anomalies of the upper cervical vertebrae occur more frequently in individuals with grooved tongue, cleft lip, cleft palate.[17,18] The presence of a fixed torticollis may hide a hypoplasia of the atlas in childhood.[17] In their study, Currarino et al. subdivided the patients into five clinical groups: 1) asymptomatic and incidental findings, 2) neck pain or stiffness after trauma to the head or neck, 3) chronic symptoms referable to the neck, 4) various chronic neurological problems, and 5) acute neurological symptoms after minor cervical trauma.[12] In the literature, all the case reports highlight the role of this abnormality in the development of cervical myelopathy. In most of the published cases, an MRI was not performed due to the absence of neurologic symptomatology.[3,4] In symptomatic patients, an MRI is able to depict the secondary changes within the spinal cord such as myelomalacia, cord edema, a presyrinx state or myelopathy due to cervical stenosis.[19,20] Richardson et al. presented an intermittent quadriparesis in a 15 year-old boy and suggested that the symptoms were secondary to compression of the cord by the inward mobility of the isolated posterior bony fragment during the extension of the cervical spine.[3] Recently, most of the patients presented in the literature are children or women in their second decade of life.[19,20] All patients that presented with significant neurological findings had a type C or D anomaly.[3,4,19,20]

We described a young female patient with aplasia of the posterior arch of the atlas together with anterior rachischisis classified as type D, clinical subgroup 1, according to Currarino. We suggested that there could be a possible association between congenital abnormalities of the atlas and early disc degeneration, but our findings have not been addressed in the literature (Figure 3).[21] One patient, a 30-year-old man, presented from Sharma et al. had a disc protrusion at C5-C6 .[22] One possible explanation for early degenerative disc disease might be the altered stability of the upper cervical spine, resulting in increased forces applied to the lower levels.

Arnold-Chiari malformation
Gonadal Dysgenesis
Klippel-Feil anomaly
Down and Turner syndrome
Facial and mouth anomaly (Cleft lip, cleft palate, facial asymmetry,hemifacial microsomia, plagiocephaly, grooved tongue)
Fixed torticollis
Haematologic disorders (Thalassemia minor)

Table 3.Anatomical disorders and diseases accompanied by atlas anomaly

Dynamic MRI might be helpful for the diagnosis of cord compression from the isolated bone tubercule and may help depict patients who should avoid contact sports and other strenuous activities.

Conclusion

The anomalies of the atlas are rare and in general asymptomatic, but physicians must be familiar with their clinical presentation, which occasionally may

Congenital Defects of the Atlas: An Insidious Malformation

be complicated by dynamic cord compression. It is important to be careful when evaluating an acute neck trauma in order to perform an appropriate diagnosis and to avoid overtreatment. When this anomaly is associated with myelopathy due to cervical stenosis, surgical decompression is a good option.

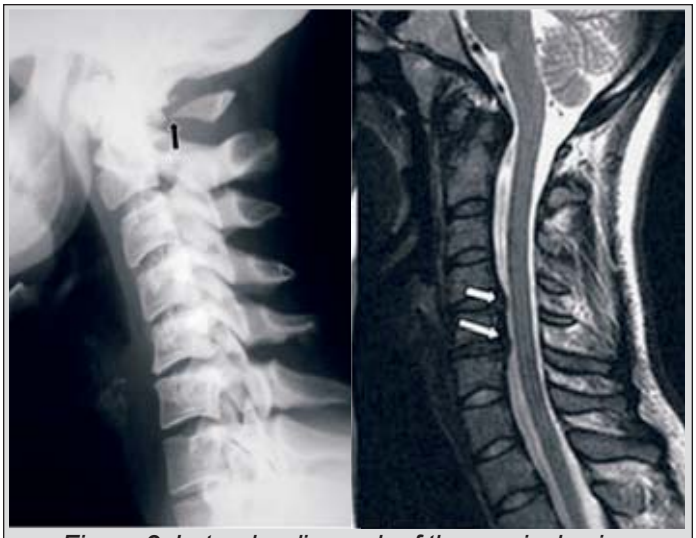

Figure.3. Lateral radiograph of the cervical spine reveals aplasia of the posterior arch of the atlas (arrow) with an isolated posterior bony fragment (Type D according to Currarino)

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Congenital Anomalies of the Cervical Spine

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Congenital cervical anomalies range from single and clinically inconsequential to multiple and complex with serious neurologic and biomechanical implications. They can occur in isolation or as part of a syndrome with other skeletal or multiorgan anomalies. Many are discovered incidentally and require no treatment. Others may require clinical and radiographic vigilance, whereas some require immediate attention. The more common anomalies seen by pediatric spine surgeons include arch defects of the atlas, assimilation of the atlas, basilar invagination/impression, os odontoideum, and Klippel-Feil Syndrome. Treatment is usually reserved for those patients whose lesions are causing or have caused neurologic injury, chronic pain, or spinal deformity or place the patient at high risk for developing these.
Keywords: Spine, Cervical abnormalities, Atlas, Odontoid abnormalities

Introduction

Congenital abnormalities of the cervical spine occur in many different forms but are usually found as sporadic, solitary cases. In some cases, they may be found as part of a skeletal or multiorgan syndrome. Many of these anomalies are asymptomatic and go undetected, requiring no treatment, but several types may result in biomechanical instability or compress neurologic structures. Because these may place a patient at risk for either neurologic injury or chronic pain from deformity, they must be monitored with observation or managed aggressively. Most lesions are identified before adulthood, but some remain undetected until later in life. Patients may have multiple coexisting osseous and neural anomalies. Some congenital anomalies may be misinterpreted as traumatic injuries, but usually they can be differentiated by the use of detailed imaging studies, lack of soft-tissue swelling and acute neurologic deficits, and lesser degrees of vertebral subluxation.[1]

Epidemiology of Congenital Disorders

The incidence of congenital disorders is difficult to quantify because many congenital abnormalities of the cervical spine are asymptomatic and the true incidence is likely largely underreported. It has been estimated that as many as 5% of fetuses have vertebral anomalies,[2] but the reported incidence in the general population is much lower. As a general estimate, some authors have reported that congenital anomalies of the cervical spine occur in approximately 1 in 40,000–42,000 births, with a slight female predominance.[3,4] Congenital fusions can occur at any level of the cervical spine, although 75% occur in the region of the first three cervical vertebrae.

Upper Cervical Spine Abnormalities

The embryology of the craniovertebral junction (CVJ) is unique and complex and produces malformations that are seen only in this region. Several developmental abnormalities may occur at the craniovertebral junction. These can result in neural compression (of the cervicomedullary spinal cord and lower cranial nerves) and vascular compromise and can manifest with abnormal cerebrospinal fluid dynamics (e.g., hindbrain herniation or Chiari I malformations). In a recent review of his extensive personal experience with children afflicted by craniovertebral anomalies, Menezes found that 80% had spastic quadriparesis, 30% had lower cranial nerve palsies, 40% had vertebrobasilar dysfunction, and 30–40% had hindbrain

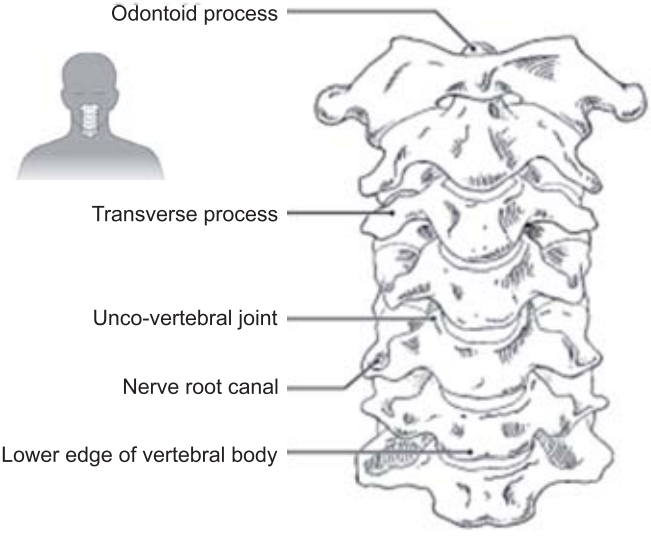

Figure 1. Front View of Cervical Spine.
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Congenital Anomalies of the Cervical Spine

herniation.[5] Hosalkar et al.[6] evaluated 68 patients with 234 osseous upper cervical spine anomalies treated during a 15-year period. In 21 patients, the anomalies were associated with a syndrome, and 79% of patients had 3 or more anomalies. Neck pain was present in 38% of patients; neurologic changes in 30%. Forty-four (65%) patients eventually required decompression and fusion of the occipitocervical junction.

Malformations of the Occipital Condyles

The proatlas, which is the fourth occipital sclerotome, develops into the anterior rim of the foramen magnum and the occipital condyles. Duplications or irregular development of the occipital condyles are rare but have been reported. A benign third condyle (condylus occipitalis) has sometimes been discovered in the midline on autopsy.[7] Abnormally enlarged condyles have also been reported. A paracondylar process, which usually has little or no clinical significance, was recently reported to be the cause of post-traumatic headaches that resolved after resection.[8]

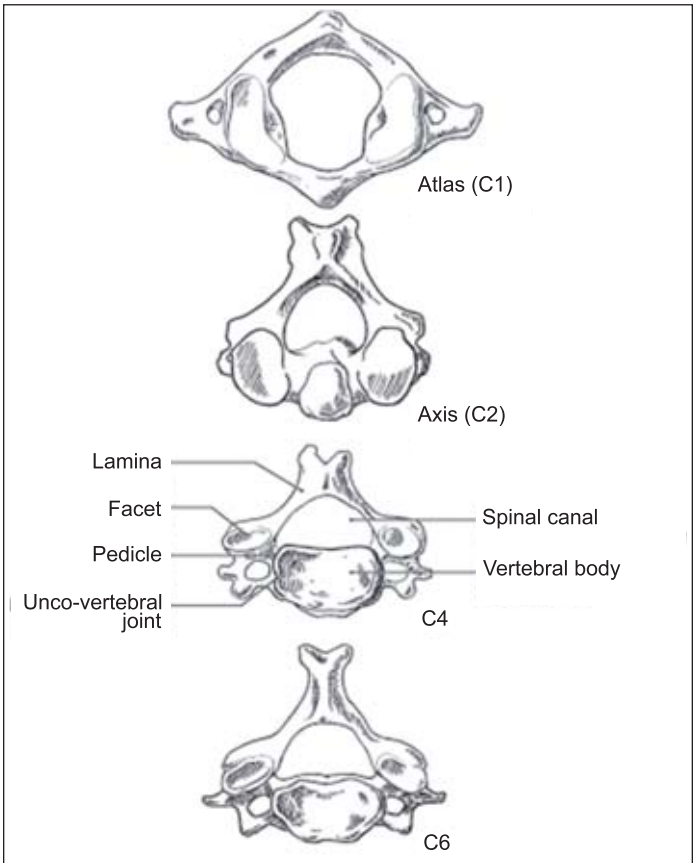

Figure 2. Cervical vertebrae from above.
Reprinted from Boden SD, McCowin PR, Davis DO et al: Abnormal cervical spine MR scans in asymptomatic individuals: a prospective and blinded investigation. 72A: 1178-1184, 1990, with permission from The Journal of Bone and Joint Surgery, Inc.

Occipitalization of the Atlas

Occipitalization or assimilation of the atlas occurs in approximately 0.25% of the population. It is characterized by fusion of the occiput to C19 and is generally defined as a failure of segmentation between the last (fourth) occipital and first cervical sclerotomes.[10] The fusion can be complete, partial, unilateral, and either bony or fibrous.[11]

Occipitalization of the atlas can occur with various syndromes, including achondroplasia, spondyloepiphyseal dysplasia, Larsen syndrome, and Morquio syndrome. As such, it usually occurs in conjunction with other anomalies, such as congenital fusion of the second and third cervical vertebrae, basilar invagination, Chiari I malformation, and Klippel-Feil syndrome, although it can be isolated.[12,13] This anomaly is also associated with a high prevalence of anomalous vertebral artery position, which must be fully detailed before any surgery is undertaken. In fact, the frequency of vertebral artery anomalies at the extraosseous and intraosseous regions is increased in any patient having osseous anomalies at the craniovertebral junction.[14] Tubbs et al.[15] found that there was an anomalous osseous pathway as the vertebral artery enters into the cranium in 80% of cadavers in which the posterior atlantal arch or hemiarch was fused to the occiput.

In most cases, the atlas and occiput are fused anteriorly with hypoplastic or anomalous posterior atlantal elements.[9,16] Many of the afflicted patients are symptomatic, likely because of instability due to a weakened or absent transverse atlantal ligament.[17] Gholve et al.[18] have recently provided a detailed radiographic and clinical analysis of 30 patients with occipitalization of the atlas. The patients were categorized based on where along the atlas the fusion occurred. Fusions were relatively equally divided among zones, but those with fusions in the lateral masses had the highest prevalence of spinal stenosis (63%). Seventeen patients (57%) had atlantoaxial instability, and eight of them (27%) had an associated C2-C3 fusion.

Neurologic symptoms in patients with occipitalization of the atlas include weakness, numbness, or pain in the upper extremities and associated up-

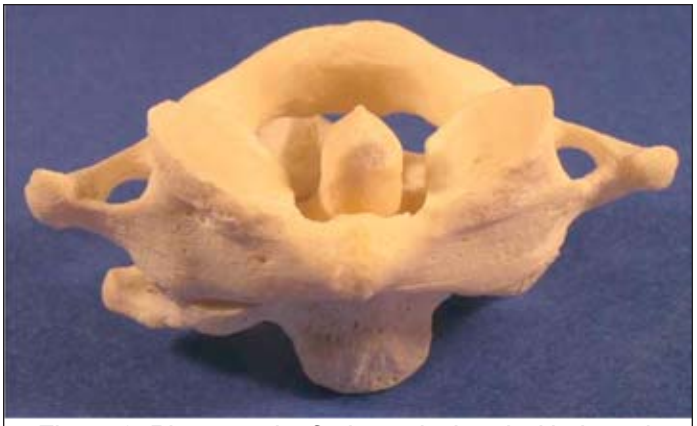

Figure 3. Photograph of atlas articulated with the axis
David B. Fankhauser, University of Cincinnati Clermont College
webpage: http://biology.clc.uc.edu/fankhauser/

per motor neuron signs including hyperreflexia and spasticity. Clinically, patients may present with a low hairline, restricted neck movements, and a short neck, all of which are also associated with Klippel-Feil syndrome (see below).[12,19]

Because of the fusion of the occiput and C1, the atlantoaxial segment can be abnormally stressed and can become unstable. The atlantoaxial segment can sustain a 'double hit' if there is also congenital fusion of the C2-C3 segment, which is not infrequent in these patients.[5,18] These stresses can lead to a reducible form of basilar invagination. Because pannus can develop around the odontoid process to limit movement, the lesion becomes irreducible as the patient ages.[5,20]

Several treatment options are available for occipitalization of the atlas. If the anterior arch of C1 is fused to the occiput without associated translation of C1 relative to C2 (which may indicate an incompetent transverse ligament), the posterior elements of C1 can be resected. Associated atlanto-occipital or atlantoaxial instability should be treated with internal fixation and fusion. In some cases, the atlantoaxial subluxation or basilar invagination can be reduced by the use of traction. If the abnormality is reducible, posterior stabilization alone is adequate.[21] If reduction is inadequate to reduce the spinal cord compression, ventral decompression with fusion and stabilization is required.[22]

Atlantal Anomalies

Various congenital anomalies affect the atlas. The normally concave C1 superior articular surface is absent in patients with Down syndrome with occipitocervical instability.[23] In some patients, the arch of C1 can be fused to C2 or completely absent, or there may be a hemi-ring.[24,25] Recently, an extremely rare case of unilateral enlargement of an atlas facet resulting in cord compression and progressive quadriparesis has been described.[26]

Various defects of the ring of C1 have been described, with posterior defects being much more common than anterior.[27,28] Evaluation using computed tomography (CT) is important because anterior or posterior ring anomalies can often be mistaken for fractures on plain films.[29,30] These anomalies alone are usually without any clinical consequence, although they are sometimes associated with other anomalies or may themselves cause myelopathy.[31,32] Hemi-rings, however, can widen as the child develops as the opening in the ring enlarges when the two hemi-rings migrate laterally. This can lead to progressive deformity, pain, basilar invagination, and myelopathy (Fig. 4).

Congenital partial aplasia of the posterior arch of the atlas is a well-described phenomenon in which a bony defect of the posterior arch of C1 is replaced with a dense fibrous band that is mobile and can repeatedly traumatize the posterior spinal cord.[33-36] Hypoplasia of the posterior arch, which effectively decreases the space available for the spinal cord, causes progressive myelopathy.[37-39] Interestingly, many patients will not present until well into adulthood.[40-43] Treatment consists of removing the posterior arch.

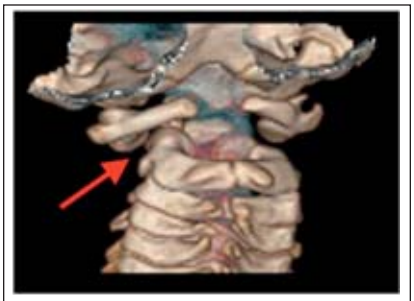

Figure 4. Posterior view of a CT-derived three-dimensional model from a young boy with multiple cervical anomalies including a hemi-ring of C1. There is 'spreading' of the lateral masses of C1 compared with the superior articulating facet of C2 (red arrow). C1 in fact barely articulates with C2 but remains in opposition with the occipital condyles. (Reprinted from: Klimo P, Rao G, Brockmeyer DL: Congenital anomalies of the cervical spine. Neurosurg Clin N Am 18:463-78, 2007, with permission from Elsevier)

The arcuate foramen (which is also known as ponticulus posticus, foramen arcuale,

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and foramen atlantoideum posterius) is an anomalous ossification of the posterolateral surface of the atlas that creates a complete or incomplete bone encirclement of the V3 segment of the vertebral artery as it exits the transverse foramen of the atlas. It also houses the vertebral venous plexus and the suboccipital nerve.[44] It is present in 5–19.3% of individuals and the incomplete type is more common.[45] This anomaly is usually of no importance except in patients who need instrumentation of C1, in particular, lateral mass screws. In these patients, identification of this anomaly is important to prevent vertebral injury during placement of the screws.[46]

Achondroplasia

Achondroplasia has a significant association with craniocervical deformities. A narrowed foramen magnum and upper cervical stenosis may be seen with CT imaging in a majority of patients.[47,48] Compression may result from hypertrophied margin of the foramen magnum, anterior extension of the squamous portion of the occipital bone into the foramen magnum, abnormal fusion of the posterior neural arch of the atlas with the posterior margin of the foramen magnum, or dense fibrotic epidural bands commonly found anterior to the posterior ring of the atlas. In patients with achondroplasia, the odontoid process often projects posteriorly and superiorly into the small foramen magnum, resulting in medullary compression.[49] There has also been a case report of overgrowth of the opisthion into the foramen magnum.[50]

Although foramen magnum stenosis is a common radiologic finding in pediatric achondroplasia patients, only a fraction of those patients will exhibit symptoms of cervicomedullary compression. For this reason, treatment decisions should be based on signs or symptoms of neurological dysfunction rather than on the radiological evaluation alone. Treatment involves suboccipital decompression with or without duraplasty to accommodate the lower brainstem and upper spinal cord and is very successful at improving or completely resolving preoperative neurologic symptoms.[51] Duraplasty is often avoided because it is difficult to achieve a water-tight closure and many children have underlying hydrocephalus, both of which increase the risk of developing a postoperative cerebrospinal fluid leak.[51]

Basilar Invagination

Basilar invagination, or cranial settling, is characterized by the encroachment of the foramen magnum by the odontoid process resulting in impaction of the cervicomedullary junction. Primary or true congenital basilar invagination is associated with other abnormalities, including atlantooccipital fusion, hypoplasia of the atlas, hemi-rings of C1 with 'spreading' of the lateral masses, Chiari I malformations, odontoid abnormalities, Klippel-Feil syndrome, and achondroplasia. Condylar hypoplasia elevates the position of C1 and C2 and often leads to basilar invagination. Acquired basilar invagination, or basilar impression, is caused by softening of the bone at the base of the skull due to osteoarthritis, Paget disease of bone, hereditary disorders of connective tissue such as osteogenesis imperfecta and Ehlers-Danlos syndrome, Hurlers syndrome, rheumatoid arthritis, tumors, or infection.[52,53]

Generally, basilar invagination can be defined by the amount of protrusion of the odontoid process through the foramen magnum. Its diagnosis traditionally involved calculating Chamberlain, McRae, or McGregor lines (Fig. 5) from lateral radiographs of the cervical spine. McRae's line from the anterior to the posterior rim of the foramen magnum defines the

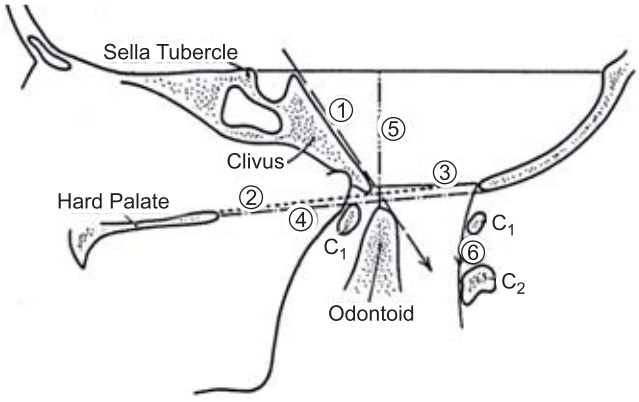

Figure 5. The various methods (craniometry) used to assess basilar invagination including Wackenheim line, Chamberlain line, McRae line, height index of Klaus, and the spinous interlaminar line. (Reprinted from: Klimo P, Rao G, Brockmeyer DL: Congenital anomalies of the cervical spine. Neurosurg Clin N Am 18:463-78, 2007, with permission from Elsevier).

opening of the foramen magnum, so an odontoid process that projects above this line is likely to induce symptoms. McRae reported that a reduction of the opening of the foramen magnum to less than 19 mm was likely to produce neurologic deficits.[9] Another option, Clark's method, essentially determines the station of atlas in relation to the odontoid process on a plain lateral radiographs.[54] The anterior ring of atlas should be adjacent to the cephalad third of the axis (station I). Mild cranial settling (station II) is present if the anterior ring is adjacent to the middle third of the axis (station II) and severe (station III) if the ring is adjacent to the bottom third of the axis. This method is simple and consistently reproducible;[55] however, although plain radiographs have their utility as screening methods, overlying skull base structures may obscure the identification of the key anatomic structures needed to determine the various measurements described. Thus, the best imaging modality is a combination of CT and MRI, which provide clear definition of the regional bony anatomy.

A new measurement that can be obtained by sagittal CT or MRI, the vertical atlantoaxial index (VAAI), quantifies the relationship between the atlas and axis in the sagittal plane based on a ratio between lines drawn on images.[56] There are several advantages to this method compared to the ones described above. The VAAI is not an absolute number but a ratio. This eliminates errors due to magnification and it can be readily applied to radiographs, CT, or MR images. In addition, the severity of basilar invagination may be classified using this ratio. A normal ratio was 0.8, mild basilar invagination was 0.6-0.71, moderate was 0.41 to 0.6 and severe was less than or equal to 0.4.

Children with basilar invagination often present with a short neck and a limited, painful range of motion; however, symptoms are highly variable and often do not become apparent until the second or third decades of life. Patients may often present with muscle weakness, neck pain, posterior column dysfunction, and paresthesias.[57] Symptoms may also be elicited by minor trauma. Other common presenting signs include localized torticollis and low hairline.[57] In one subtype of basilar invagination,[57] patients had only the radiographic finding of basilar invagination; in the other subtype, patients also had an associated Chiari I malformation.

Traction is generally used for the initial treatment of basilar invagination to reduce the compression of the neural structures by the odontoid. A posterior occipitocervical stabilization procedure can be performed to maintain the reduction. If the invagination cannot be reduced, a transoral decompression, followed by a posterior occipitocervical fusion, may be required. Patients with an associated Chiari decompression and syringohydromyelia require foramen magnum decompression with duraplasty in addition to dorsal craniocervical junction fusion.[22,57] For those patients without a concomitant Chiari malformation, Goel suggests that the treatment should be directed at the atlantoaxial joint by reducing the vertical subluxation and fusing this joint.[58]

Posterior C2 Arch Anomalies

Although they are less common than defects of C1, posterior C2 arch defects are often more problematic because they must be differentiated from traumatic spondylolisthesis and persistent neurocentral synchondrosis.[59,60] Defects are generally characterized by sclerosis of the fragments that separate on flexion and malformation or underdevelopment of the posterior arch of C2.[61] Trivedi et al.[62] reported a case in which the patient had complete absence of the posterior elements of C2 and excessive motion between C2 and C3. The patient was treated with an occiput to C3 fusion.

Dysplastic or hypoplastic posterior arches of C2 may cause myelopathy. The clinical and radiographic picture is similar to that of hypoplastic posterior arch of C1 in that the arch is often bifid and invaginating into the spinal canal, many patients present in adulthood, and treatment entails performing a laminectomy.[63-65]

Anomalies of the Odontoid

Congenital abnormalities of C2 often involve some malformation of the odontoid process ranging from hypoplasia to complete aplasia.[19,66] The resultant clinical picture may be one of atlantoaxial instability because the normal anatomic and biomechanical complex involving the transverse cruciate ligament and an intact odontoid process are not present. The odontoid may also be misshapen, in particular angled posteriorly (retroflexed) and in association with hindbrain herniation (Fig. 6). Tubbs et al.[67] found that a retro-

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flexed odontoid was associated with syringomyelia and particularly holocord syringes and higher grades of angulation were more common in female patients and with greater degree of caudal displacement of the fourth ventricular obex. The true incidence of C2 anomalies is unknown, but they are seen in association with Down syndrome, Morquio syndrome, and other skeletal dysplasias.

Os odontoideum is a dissociation between the body of C2 and the dens, such that a disconnected ossicle takes the place of an intact odontoid process. Currently, most authors believe this dissociation has a traumatic cause, perhaps minor, that disrupts the vascular supply of the developing dens in childhood, causing it to dissociate from the axis, although some authors favor a congenital cause.[68-70] This chronic nonunited fracture should be differentiated from os-siculum terminale persistens, in which the tip of the dens, the ossiculum terminale, fails to fuse with the remainder of the dens. The ossiculum terminale usually is firmly bound to the main body of the dens by cartilage and consequently is seldom the source of instability.

Dynamic imaging with flexion/extension films should be obtained to identify any instability and MRI should be obtained to evaluate the spinal cord. Treatment for atlantoaxial instability resulting from os odontoideum or a maldeveloped odontoid process usually requires posterior stabilization. The highest success rates have been achieved with a C1-2 transarticular screw fixation method.[71] Some authors, including ourselves, have also argued that even in the setting of asymptomatic instability, patients should undergo a fusion procedure because even minor trauma may result in a significant neurological injury.[72,73] We recently reported on three patients with a known os odontoideum who did not undergo any stabilization initially and subsequently suffered a spinal cord injury.[72] All three underwent a posterior C1-2 transarticular screw fixation and fusion with good outcome.

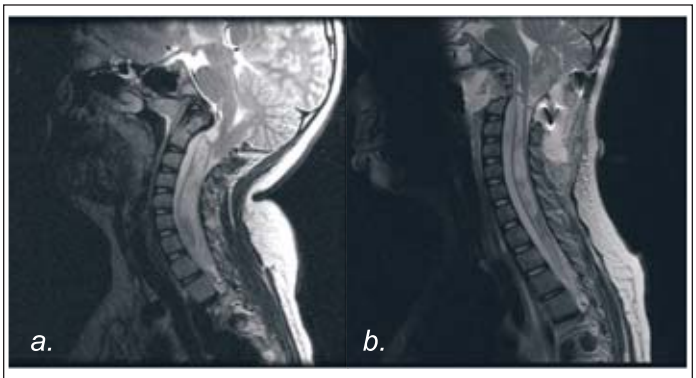

Figure 6. This patient has a retroflexed odontoid with ventral cervicomedullary compression (a). There is also a Chiari I malformation, a large syrinx throughout the cervical cord and platybasia. After a transnasal odointoidectomy and posterior fossa decompression with occipitocervical stabilization and fusion, the cervicomedullary junction and foramen magnum are decompressed and the size of the syrinx has substantially decreased (b).

Subaxial Spine Abnormalities

Klippel-Feil Syndrome. In 1912, Klippel and Feil reported the case of a patient with a short neck, low hairline, and limited neck mobility[74] who was found to have only 12 discernible vertebrae on autopsy. Klippel-Feil Syndrome (KFS) refers to any congenital fusion of the cervical spine of two or more cervical vertebrae.[75] The most commonly fused level is C2-3[76]. Despite the initial description, it is now recognized that fewer than 50% of patients with congenital fusion of the cervical spine will have the triad of classic characteristics.[3] The incidence is estimated to be approximately 1:40,000–42,000 births[3,77] and it may be the most commonly encountered congenital malformation of the cervical spine. Other abnormalities associated with KFS include congenital scoliosis, rib abnormalities, deafness, genitourinary abnormalities, Sprengel deformity, synkinesia, cervical ribs, and cardiovascular abnormalities.[78-82]

Because Feil's subdivision of the syndrome into three types on the basis of the site and extent of the congenital fusion has not proven clinically useful, other classification schemes have been presented. One scheme was developed to describe three patterns of potentially unstable fusions:[80,83] fusion of C2 and C3 with occipitalization of the atlas; a long cervical fusion with an abnormal craniocervical junction; or two segments of block fusion separated by a single nonfused interspace. Other authors have correlated various KFS deformities with dynamic imaging to create a classification scheme.[84] The most recent classification separates KFS into four classes and incorporates the mode of inheritance.[85]

The most common clinical presentation of KFS is limited range of motion, particularly lateral bending. If fewer than three cervical vertebrae are fused, however, motion of the cervical spine may appear normal because adjacent levels may compensate. Thus, patients with more extensive neck fusions may present at an earlier age. Similarly, higher fusions near the craniovertebral junction often present earlier with pain whereas those with lower cervical fusion present later, when symptomatic junctional degeneration develops.[86] Samartzis et al.[87] have shown that involved segments between C2 to T1 often become completely fused (demonstrating bridging bone both anteriorly and posteriorly) as children age. Conversely, the upper cervical segments do not show such a pattern. Instead, fusion of the posterior elements was more common than fusion of the anterior elements. The same authors also found that congenital fusion may arrest the normal vertebral development as these levels tended to have greater canal dimensions (space available for the cord) and the cephalad-to-caudal dimension of the vertebral bodies was less.[88]

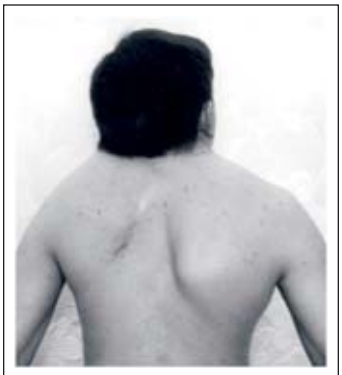

Figure 7. Klippel-Feil Syndrome
From Audiological abnormalities in the Klippel-Feil syndrome, J M McGaughran, P Kuna, V Das. Courtesey of Archives of Disease in Childhood Courtesy of BMJ Publishing Group Ltd.

Basilar invagination is also known to occur with KFS. Samartzis et al.[76] found that the risk of having the odontoid more than 4.5 mm above McGregor's line was dramatically increased if four or more segments were fused or if there was a cervical scoliosis (cervical imbalance) of greater than 10°. Torticollis or neck webbing is seen in only 20% of patients with KFS[80,89-91] but is also associated with hemivertebra of the atlas, posterior fossa tumors, infections, and cervicothoracic scoliosis.[92] In patients with severely limited neck mobility and a low posterior hairline, iniencephaly should be suspected. Facial asymmetry may be associated with cervical spine anomalies[93] and hearing loss can be present in up to 30% of patients with KFS.[90,91] Other associated syndromes include Wildervanck, Rokitansky-Kuster-Hauser, or Goldenhar syndromes.

Numerous musculoskeletal anomalies are associated with KFS, the most common being scoliosis (usually congenital), which occurs in up to 60% of patients. Sprengel deformity, a congenital elevation of the scapula, can be seen in 20% to 35% of patients with KFS. An osseous, cartilaginous, or fibrous connection between the scapula and the lower cervical spine is present about 50% of the time. Recently, Mooney et al.[82] described an osseous structure extending from the medial scapula to the clavicle and occipital region of the skull associated with a Sprengel deformity. The Sprengel deformity is thought to arise from failure of descent of the scapula from the first embryologic cervical level to its normal position, just caudal to the first rib.[94] Other musculoskeletal anomalies include cervical ribs, rib anomalies, and hemivertebrae.

Neurologic disturbances associated with KFS include developmental abnormalities of the central nervous system, such as brainstem malformations, myelopathy as a result of long-standing spinal cord compression, radiculopathy as a result of nerve root irritation, and nonspecific symptoms of headache, weakness, and numbness. Up to 20% of patients with KFS will exhibit synkinesis, in which involuntary mirrored motions, primarily in the upper extremities, are observed.[95,96] Its cause is unknown, but autopsy results of two patients with KFS and synkinesia showed an incomplete pyramidal decussation. Synkinesia is generally effectively treated with occupational therapy, and the condition often subsides as the patient ages.

Cardiovascular abnormalities are reported to occur in up to 14% of patients with KFS. Genitourinary abnormalities are also associated with KFS, affecting up to 64% of patients, with the most common manifestation being unilateral renal agenesis.[80,97,98] Abnormalities noted in the renal system may point to abnormalities of the reproductive system, particularly in females.

Routine plain radiography consisting of anteroposterior, lateral, and open-mouth odontoid views can be used to quickly identify an obvious congenital fusion or cervical stenosis. Flexion and extension views provide a dynamic snapshot to identify instability of the atlanto-occipital, atlantoaxial, and subaxial joints, although radiography of the cartilaginous spine of children younger than 8 years of age can be

Congenital Anomalies of the Cervical Spine

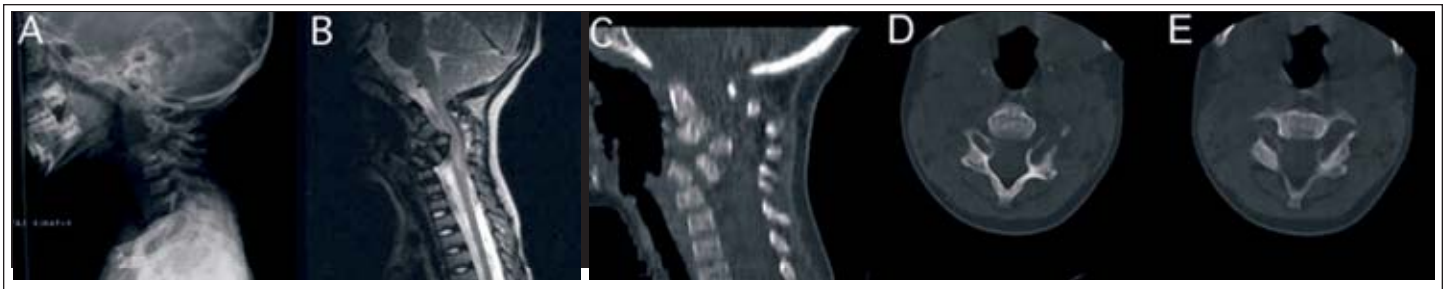

Figure 8. Lateral radiograph (A) and sagittal CT (C) depict the 'buckling' deformity of the neck with the spinal cord being compressed ventrally as shown in the sagittal MRI (B). The absence of an osseous bridge between the anterior and posterior elements and the enlarged and abnormally shaped foramen transversarium are seen in the axial CT scans (D, E).
(Reprinted from: Klimo P, Rao G, Brockmeyer DL: Congenital anomalies of the cervical spine. Neurosurg Clin N Am 18:463-78, 2007, with permission from Elsevier).

difficult to interpret. MRI should be used in the setting of suspected compromise of the brainstem or spinal cord and to detect other central nervous system lesions such as syringomyelia, tethered cord, diastematomyelia, and Chiari malformation.[3,99] Further imaging of the thoracic and lumbar spine is warranted in patients with KFS to identify abnormalities in these regions.[77]

Because many patients are asymptomatic throughout life, treatment for KFS must be individualized. For patients with atlanto-occipital instability, occipitocervical fusion should be performed. Atlantoaxial instability is best approached with C1-2 transarticular screw fixation techniques. Patients with subaxial instability typically will not present with neurological symptoms but may have significant degenerative disc disease. These patients may be successfully treated with discectomy and fusion. Cervical stenosis is generally treated with posterior decompression and fusion if necessary.[100,101]

Syndromes

Numerous syndromes have cervical anomalies among their key features. We will briefly discuss the more common ones.

Down Syndrome. Down syndrome, or trisomy 21, is the most common inherited chromosomal disorder in humans. The craniovertebral joints may be unstable in these patients for a variety of reasons. Lack of a concave C-1 superior articulating surface in conjunction with a failure to develop the curved architecture in the occipital condyle results in a flat or "rocker bottom" joint.[23,102] The atlantoaxial joint may be rendered unstable as a result of a lax transverse ligament or with the presence of an os odontoideum.[72]

Larsen Syndrome. In 1950, Larsen described a series of patients that had distinctive facial features, dislocations of multiple joints, and spinal anomalies.[103] The spinal manifestations include scoliosis, spinal stenosis, abnormal segmentation, neural arch defects, coronal cleft vertebrae, hemivertebrae, and anteroposterior dissociation. Dramatic midcervical kyphosis is often present and can lead to instability, progressive myelopathy, weakness, and even sudden death in Larsen syndrome.[104,105]

Goldenhar Syndrome. Goldenhar syndrome, also known as oculoauriculovertebral dysplasia, is a clinically heterogeneous disorder characterized by hemifacial microsomia, epibulbar dermoid appendages, and spinal defects. Segmentation defects (block vertebrae) are common in the cervical spine, whereas formation defects (hemivertebrae) are more common in the thoracic spine, leading to scoliosis. Other anomalies include basilar invagination, retroflexed odontoid, assimilation of the axis, and odontoid hypoplasia leading to atlantoaxial instability.[106,107]

Spondyloepiphyseal Dysplasia. Spondyloepiphyseal dysplasia (SED) encompasses several disorders characterized by abnormal growth of the spinal vertebrae and epiphysis. Atlantoaxial instability associated with odontoid hypoplasia or ligamentous laxity is the most common spinal manifestation of SED in children.[108]

Morquio Syndrome. Mucopolysaccharidosis type IV (MPS IV), or Morquio syndrome, is an autosomal recessive lysosomal storage disease characterized by an inability to metabolize keratan sulfate, a glycosaminoglycan found predominantly in cartilage and in the cornea. As in SED, the most common cervical

manifestation is atlantoaxial instability due to odontoid dysplasia (hypoplasia, aplasia, os odontoideum) or ligamentous laxity.[109,110]

Miscellaneous Disorders

Formation–segmentation anomalies can occur in the cervical spine as they do in other parts of the spine. These can be found in isolation or in combination with other spinal anomalies and include midline vertebral body clefts, sagittal and coronal hemivertebrae, hypoplasia or complete absence of a vertebrae, absence or malposition of a pedicle, hyperplasia of the spinous process, and block vertebrae (most commonly between C2 and C3).[111-115]

Cervical spondylolysis, which is a cleft between the superior and inferior articular facets of the articular pillar or lateral mass, the cervical equivalent of the pars interarticularis of the lumbar spine, is a rare congenital spinal anomaly.[116-119] Characteristic radiographic findings include well-corticated margins at the defect, a characteristic "bow-tie" deformity, and ipsilateral dysplastic facets. Compensatory hypertrophic changes of the adjacent articular processes, spina bifida, and spondylolisthesis are frequently seen.[120] Cervical spondylolysis most commonly occurs at a single level (the most common level is C6), but several cases of multilevel involvement have been reported.[119,121-125]

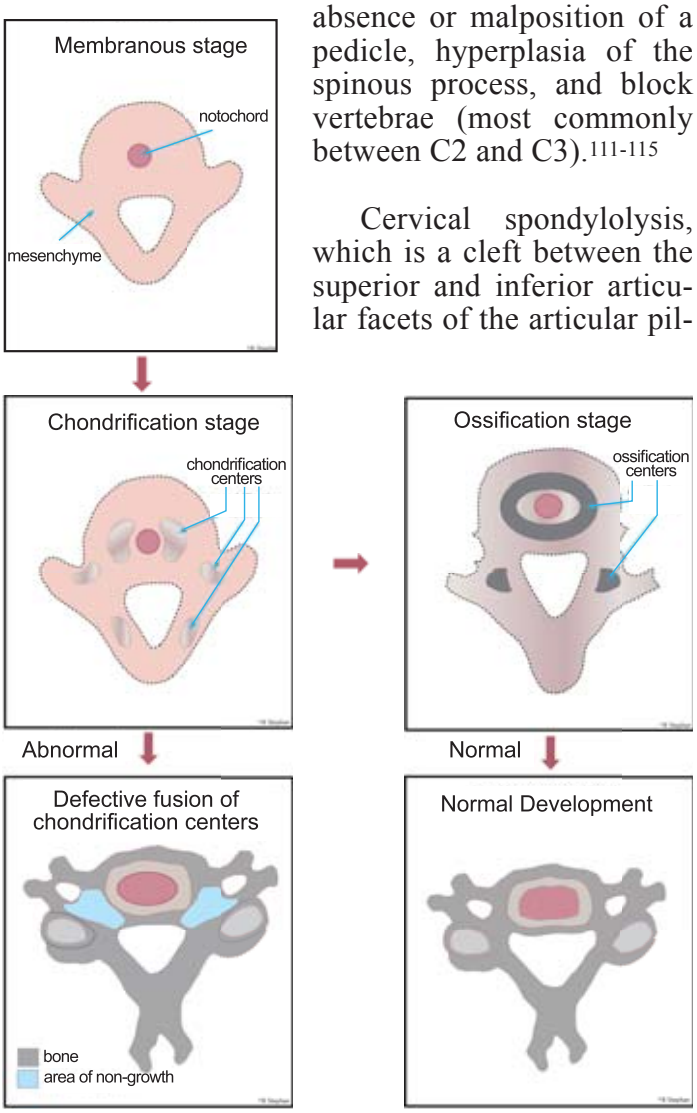

Figure 9. The normal chondrification and ossification stages of spinal embryogenesis. The anomaly is due to improper fusion of chondrification or ossification centers.
(Reprinted from: Klimo P, Rao G, Brockmeyer DL: Congenital anomalies of the cervical spine. Neurosurg Clin N Am 18:463-78, 2007, with permission from Elsevier)

Congenital multilevel cervical disconnection syndrome is a newly described syndrome in which there is an osseous disconnection between the anterior and posterior elements resulting in a severe kyphotic deformity and myelopathy. (Fig. 8).[153]

Patients require extensive anterior and posterior reduction, decompression, reconstruction, and stabilization/fusion procedures. The pathology is thought to be due to failure of connecting chondrification centers to form (Fig. 9).

Summary

Developmental anomalies of the cervical spine vary widely. Patients may present with abnormalities as simple as two congenitally fused vertebrae requiring no treatment, or as complex as craniocervical instability requiring occipitocervical fusion. It is important to recognize that some of these malformations may be associated with other defects involving the cardiovascular, neurological, renal, and reproductive systems. The true incidence of these anomalies is not known for certain, partly because of their frequent asymptomatic nature. Identifying the symptomatic anomalies requires adequate imaging. Recognizing those congenital abnormalities that contribute to an unstable cervical spine or critical spinal stenosis may prevent a catastrophic spinal cord injury.

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Congenital Anomalies of the Cervical Spine

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The Genetics of Intervertebral Disc Degeneration

Leonid Kalichman, P.T., Ph.D.

Intervertebral disc degeneration (IDD) can contribute to the development of low back pain and acute lumbar radiculopathy. The dramatic change in the concept of risk factors for IDD from one where age and mechanical factors were paramount to the current theory that genetic risk factors are predominant made it important to review the studies of the genetic influences on IDD beginning with familial aggregation and heritability estimation and finishing with specific studies of genes associated with IDD.

Methods: Narrative review of English language medical literature.

Results and Conclusions: Prior research has demonstrated the existence of familial predisposition to IDD with a heritability range 34-75% in different spine locations. Segregation analysis shows that the mode of inheritance is complex with multiple factors and multiple genes likely involved in intergenerational transmission. There are a number of genes that have been associated with IDD in humans, including genes coding for collagen I, collagen IX (COL9A2 and COL9A3), collagen XI (COL11A2), IL-1, aggrecan, vitamin D receptor, MMP-3, and CILP. For specific genes and some environmental factors, gene–gene, gene–environment and gene-age interactions may exist. Candidate-gene association studies have limitations in detecting the genetic basis of the disease because this approach relies on having predicted the correct genes on the basis of biological hypothesis or the location of the known linkage regions. Additional studies, including linkage analyses and whole genome scan studies in different populations and whole range of ages, are required to better understand the influence of aforementioned genes on IDD and probably to find new candidate genes. *Keywords:* intervertebral disc degeneration, heritability, genes, spine

Degenerative changes in intervertebral discs can contribute to the development of low back pain (LBP) and acute lumbar radiculopathy associated with disc herniation.[1,2] MacGregor et al.[3] first demonstrated a clear association in a sample of female twins between disc degeneration (evaluated by magnetic resonance imaging (MRI)) in the lumbar spine and the propensity to report pain in the lumbar spine. They concluded that those associations were mediated genetically.

There is a fundamental problem in the investigation of intervertebral disc degeneration (IDD). First, there is no standard definition of IDD, probably because the phenomenon itself is not fully understood. Conceptually, disc degeneration is a product of lifelong degradation with synchronized remodeling of discs and neighboring vertebrae, including simultaneous adaptation of the disc structures to changes in physical loading and responses to the occasional injury.[4]

Operationally, IDD is defined largely by the method of evaluation. Radiographic data have been widely used, especially before the advent of MRI. In addition to the information gained from microscopic, histologic, or biochemical analysis, surgical and autopsy samples can provide a macroscopic measurement of degeneration.[5] However, the currently preferred method of IDD evaluation is MRI, because it allows simultaneous evaluation of various phenomena (such as disc-space narrowing, bulging, or signal intensity loss) with the use of ordinal scales. In a recent comprehensive review, Adams and Roughley[6] gave the following definition of IDD: "The process of disc degeneration is an aberrant, cell-mediated response to progressive structural failure". A degenerate disc is one with

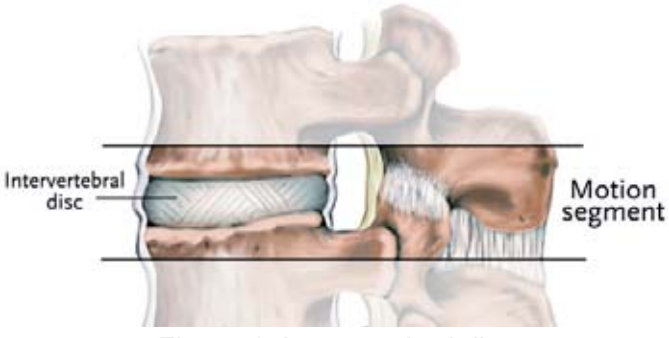

Figure 1. Intervertebral disc
Courtesy of Medtronic

structural failure combined with accelerated or advanced signs of aging. Early degenerative changes should refer to accelerated age-related changes in a structurally intact disc. The term, 'degenerative disc disease', should be applied to a degenerate disc that is also painful.

In a MRI study of lumbar intervertebral discs, the prevalence of degenerative intervertebral discs was shown to increase linearly with age, and by 70 years of age, 80% of all lumbar discs were abnormal.[7] The exact pathophysiological mechanism is, however, still unclear. Age, heavy physical loading, injury, vibration, infection and smoking have been reported to be risk factors.[8-10] However, the results of recent studies suggest that genetic factors/heredity have a dominant role in IDD and herniation.[11] The review article by Battié et al.[12] concluded with the following statement: "the genetically determined 'natural progression of disc degeneration' is modified to some degree by behavioral and environmental factors". Adams and Roughley[6] defined the underlying cause of IDD as tissue weakening, occurring primarily from genetic inheritance, aging, nutritional compromise, and loading history.

It is still uncertain whether a specific gene effect of relatively large magnitude exists or whether the genetic contribution is due to small effects of many genes. However, it appears likely that disc degeneration may be characterized as a common, oligogenic, multifactorial genetic condition.[4] To date, several gene loci associated with human IDD have been identified, and others, representing the most significant genetic susceptibility, have yet to be identified. Hereditary factors could affect disc degeneration through several mechanisms, such as an influence on the size and shape of spinal structures that affect the spine's mechanical properties and thus its vulnerability to external forces. Biologic processes associated with the synthesis and breakdown of the disc's structural and biochemical constituents could be partly genetically predetermined, leading to accelerated degenerative changes in some persons, relative to others. The identification of specific genetic influences may eventually provide key insights into underlying mechanisms. Furthermore, for specific genes and some environmental factors, gene-gene interactions and gene-environment interactions may exist.

This dramatic change in the view of risk factors for IDD from one where age and mechanical factors were paramount to the current theory of predominance of genetic risk factors made it important to review the studies of the genetic influences on IDD, beginning with familial aggregation and heritability estimation and finishing with specific studies of genes associated with IDD. An up-to-date knowledge of the genetic influence on IDD may be helpful in the development of early diagnostic and prevention tools for lumbar and cervical disc degeneration and also in the determination of future research goals.

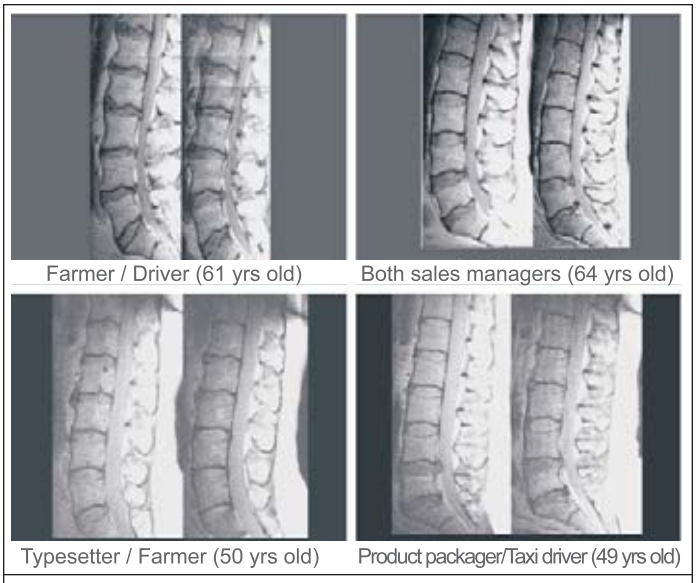

Figure 2. Spine MRIs of pairs of twins show similarity in disc degeneration despite differences in occupation (Reprinted from Battié et al., The Twin Study: Contributions to a Changing View of Disc Degeneration, The Spine Journal, 9 (2009) 47–59, with permission from Elsevier).

Methods

PubMed, CINAHL, PsichInfo and ISI web of Science databases were searched from inception until November 2008 for the key words: "degenerative disc disease", "disc herniation", "disc protrusion", "disc extrusion", "intervertebral disc", "lumbar spine", "low back pain", "gene", "heritability", "twin studies". All relevant articles in English were reviewed. Pertinent secondary references were also retrieved. We critically analyzed all published material. We also consulted experts in genetic epidemiology, rheumatology and orthopedic surgery to produce this narrative review of genetic factors in intervertebral disc degeneration.

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Results and Discussion

Familial predisposition studies. Evaluation of the familial aggregation of the studied condition (phenotype) is usually the initial stage of assessment of a genetic influence hypothesis. The first descriptions of familial predisposition for lumbar disc degeneration (LDD) were in juvenile and adolescent populations. Grobler et al.[13] mentioned a positive family history in seven of 29 adolescents with disc herniation. Later studies suggested a familial predisposition for lumbar disc herniation in juvenile patients.[14,15] More recently, 43.8% of patients under 17 years old with lumbar disc herniation had a positive family history.[16] Study of juvenile lumbar disc herniation is especially interesting because, in young patients, such important risk factors as age, smoking and occupation will have had little, if any, impact on disease predisposition. Genetic predisposition, and possibly, athletic involvement[13,17] are the most important risk factors in this age group. On the other hand, we cannot be sure that juvenile lumbar disc herniation and adult IDD and LDD are etiologically related conditions even though they are phenotypically similar and involve the same structure of the body (at both a macroscopic and microscopic level).

Familial history was also found to be a predisposing factor for LDD in adults. A survey study of first degree relatives[18] found a strong familial predisposition to discogenic LBP and to disc surgery in an adult population. In a group of individuals with discogenic LBP, 35% of families had at least one member with a history of discogenic LBP and 5% had one or two members who had undergone disc surgery. In a group of individuals who had undergone lumbar disc surgery, these numbers were 37% and 10%, respectively. Of the group of asymptomatic subjects, only 12% had at least one or more affected relatives and 1% had a relative who had undergone disc surgery.

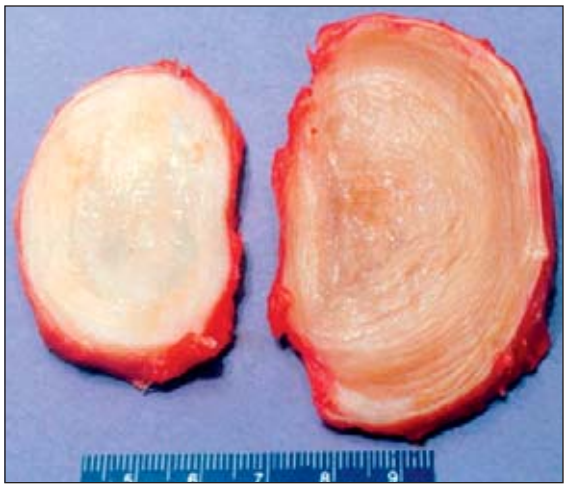

Figure 3. Photograph of normal (left) and degenerative human L2-3 intervertebral discs.
Courtesy of James C. Iatridis, PhD at the University of Vermont http://www.cems.uvm.edu/~iatridis/research/

Simmons et al.,[19] in a retrospective case-control study, found that 44.6% of a group of 65 patients who had undergone surgery for LDD had a positive family history vs. 25.4% of the control group (N=67). A history of spinal surgery was found in 18.5% of relatives in the study group, compared with only 4.5% of the control group. Richardson et al.,[20] in a similarly designed study, found that 28% of immediate relatives of patients with surgically proven lumbar disc herniation (n=60) and only 2% of relatives of individuals in a control group (n=41) met questionnaire criteria for discogenic LBP; 12% of the relatives in the studied group and no relatives in a control group had received surgical therapy for discogenic LBP. Matsui et al.,[21] using MRI and plain radiography, compared 24 patients with present or past LBP and/or leg pain and immediate relatives of the patients who had undergone surgery for disc herniation to 72 age- and gender-matched outpatients who reported LBP and/or leg pain without a family history of operated disc herniation. They found that the prevalence of disc degeneration at L4-L5 and L5-S1 was similar in cases and controls, however, the grade of IDD was significantly more severe in cases. The incidence of disc herniation/diffuse bulge was also significantly higher in cases than that in controls. A Croatian case-control study[22] comparing 67 subjects who underwent surgery for lumbar intervertebral disc herniation at L4-L5 or L5-S1 to 268 matched controls found that individuals with a positive family history showed a four-time higher risk for lumbar intervertebral disc herniation severe enough to require surgery of the lower spine.

Because monozygotic (MZ; or identical) twins have identical genes and dizygotic (DZ; or non-identical) twins have, on average, only half their genes in common, twin studies can provide invaluable tools for examining the influence of genetic factors on quantitative human traits by comparing similarities of MZ and DZ twins.[23] Results from a male MZ twin pair's

study[24] of healthy volunteers demonstrated substantial familial aggregation of LDD. In this study, the degree of similarities in degenerative findings (evaluated by MRI) by spinal level in the lumbar discs of 20 pairs of MZ twins (age 36-60) was assessed relative to what would be expected by chance based on the prevalence of the findings by level among all 40 subjects. Whereas smoking status and age explained 0-15% of the variability in the various degenerative findings in the discs, 26-72% of the variability was explained with the addition of a variable representing co-twin status. Results suggested a substantial familial influence on lumbar disc-height narrowing, bulging, herniation, and disc desiccation.

All aforementioned studies provide solid evidence for the existence of familial predisposition for LDD. Familial predisposition was found in two different but related phenotypes: 1) in individuals that underwent surgery of the lower spine due to lumbar intervertebral disc herniation, i.e. suffered from severe degeneration; and 2) in a sample of healthy volunteers, i.e. healthy volunteers and symptomatic subjects may represent different ends of a spectrum of IDD. Therefore, familial history must be an essential part of anamnesis of individuals suffering from LBP and can strengthen a clinical diagnosis of LDD. Family history may also provide a cost-effective means of identifying high-risk individuals who could benefit from aggressive preventive strategies.[20]

Heritability estimation. After obtaining the evidence for familial predisposition in development of IDD, the next step is to distinguish between genetic and environmental sources of familial aggregation, as well as to estimate the heritable proportion of IDD variability.

In a retrospective cohort study of 115 pairs of male MZ twins, lumbar MRIs were assessed to investigate the relative effects of age, suspected environmental risk factors for LDD, and familial aggregation on disc bulging, disc height narrowing, and disc desiccation (as indicated through signal intensity).[25] In a multivariate analysis of the T12-L4 region, physical loading exposures explained 7% of the variance in summary LDD scores; an additional 9% was explained by age, and another 61% by familial aggregation. In the L4-L5 and L5-S1 region, measures of occupational and leisure physical loading explained only 2% of the variance in LDD summary scores. An additional 7% was explained by age and another 34% by familial aggregation. The authors suggested that the differences in explained variance in IDD in the lower lumbar region (43% in total) compared with the upper lumbar region (77% in total) "may be a result of the possible interaction of mechanical forces with spinal anthropometrics in such a manner that it has a disproportional effect on the lower lumbar levels. The consistent finding that L4-S1 lumbar discs are more degenerated than are L1-L4 discs suggests that lifetime physical exposures have a role in disc pathogenesis because pure aging genes and all systemic factors would be expected to affect all discs similarly."[4]

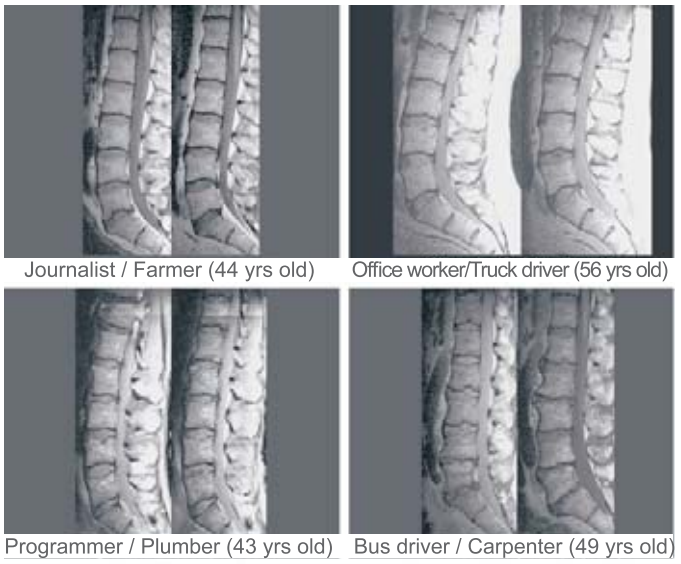

Figure 4. Spine MRIs of pairs of twins show similarity in disc degeneration despite differences in occupation (Reprinted from Battié et al., The Twin Study: Contributions to a Changing View of Disc Degeneration, The Spine Journal, 9 (2009) 47–59, with permission from Elsevier).

Sambrook et al.[23] conducted a classic twin study to determine the extent of genetic influences on IDD. They compared MRI features of disc degeneration in the cervical and lumbar spine of 172 MZ and 154 DZ twins who were unselected for back pain or disc disease (mean age 51.7 and 54.4, respectively, 80% of whom were female, from Australian and British twin registries). An overall score for disc degeneration was calculated as the sum of the grades for disc height, bulge, osteophytosis, and signal intensity at each level. An "extent of disease" score was calculated as the number of levels affected. After adjustment for

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age, weight, height, smoking, occupational manual work, and exercise, the overall heritability was 74% (95% CI: 64-81%) at the lumbar spine and 73% (95% CI: 64-80%) at the cervical spine. For "extent of disease," heritability was 63% at both sites. An analysis of the individual MRI findings suggested that disc bulging and height were the primary contributors to the genetic determination of the overall score. Bijkerk et al.[26] estimated the genetic influence on the occurrence of IDD in a random sample of 1,583 individuals from the general population. They observed that IDD was significantly more frequent in siblings than in the random sample. After adjustment for age, sex, BMI and bone mineral density, the heritability estimate for IDD was statistically significant (H= 0.75, 95% CI: 0.30-1.00). This approximates the estimates in the aforementioned studies and underlines the high heritable component for IDD.

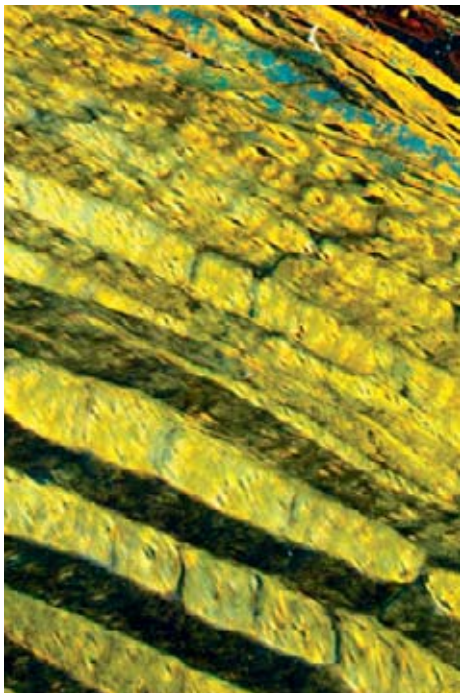

Figure 5. Transverse view of a human disc anulus fibrosus under polarized light
Courtesy of the Bone & Joint Research Laboratory

Livshits et al.[27] performed a complex segregation analysis of multiple disc herniations evaluated by computed tomography or MRI on 221 individuals belonging to six complex Arabic pedigrees. Heritability estimates for multiple disc herniations was 0.73, adjusted for sex, age, weight, and smoking. Results of the segregation analysis rejected the model of inheritance assuming major gene effect and Mendelian transmission of susceptibility to multiple disc herniations, indicating a more complex mode of intergenerational transmission.

Associated genes. Having demonstrated the substantial genetic influence on intervertebral disc degeneration, the mechanisms of the genetic effect needs to be addressed. Each disc consists of three major elements: the cartilaginous end-plates, the annulus fibrosus, and the nucleus pulposus. Parts of vertebral bodies proximal to the disc can also be involved in pathogenesis of IDD, as in the case of subchondral bone in osteoarthritis.

Two approaches have typically been used to map genetic variants: linkage analysis and association studies. Families with multiple affected individuals and multiple generations are used in linkage analysis to detect genetic regions that are more likely to be associated with the disease than would be expected by random chance. Linkage analysis is the most effective means for mapping single gene "Mendelian" diseases with high penetrance but has limited success in identifying polygenic disease genes because the statistical power is diluted with the increasing number of genes involved. Nevertheless, if one can collect a sufficient number of families with multiple members with early onset IDD, then a linkage study on these families might have adequate power to detect novel genes for IDD since these families are likely to have a significant genetic disposition for IDD.[59] Our literature search uncovered only one study[28] trying to identify IDD associated genes.

However, there are a number of genes that have been associated with degenerative disc disease in humans (Table 1), including genes coding for collagen I (COL1A1),[29,30] collagen IX (COL9A2 and COL9A3),[28,31-40] collagen XI (COL11A2),[34,38] interleukin 1 (IL-1),[41,42] interleukin 6 (IL-6),[34] vitamin D receptor (VDR)43-48, aggrecan49-51, matrix metalloproteinase 3 (MMP-3)[34,45,52] and cartilage intermediate-layer protein (CILP).[42,53] At present, only the associations of the COL1A1, COL9A2, MMP-3 and VDR genes with IDD have been verified in different ethnic populations. Among the possible reasons for the replication deficiency is the complexity of the IDD process, differences in phenotypes used in genetic studies, and differences in sample sizes. For example, the association between COL9A3 and IDD was found in a Finnish population by two different research groups[35, 38] that used MRI to define the phenotype of IDD. However, no association was found in a Greek population[32] based on x-rays and/or back surgery as an IDD phenotype. The lack of association may be due to the differences in subject ethnicity or IDD phenotypes.

Another factor to be considered is the age of the subjects. It is possible that a particular gene is associated with IDD only at a certain age. Takahashi et al.[52] found that 5A5A and 5A6A genotype of MMP3 gene in the elderly was associated with a significantly larger number of degenerative IDD than the 6A6A genotype ($p<0.05$), but there was no significant difference in young persons. The products of these genes probably affect the strength of skeletal tissues, and their systemic effects may explain why disc degeneration is more prevalent in those with osteoarthritis.[54]

Intervertebral discs contain an abundant extracellular matrix of proteoglycans and collagens.[1] The outer layer, the annulus fibrosus, consists mainly of collagen I. The interior structure of the disc, the nucleus pulposus, is about 50% proteoglycan (mainly aggrecan) and 20% collagen II. Both contain small amounts of collagen IX and XI. Results of mice studies indicate that mutations in collagen IX and aggrecan can cause age-related disc degeneration and herniation.[51,55] Collagen IX and XI are attractive candidates for lumbar disc degeneration because they serve as a minor components in structures of the intervertebral disc[1]: the annulus fibrosus and the nucleus pulposus.

Another gene that potentially could be involved in IDD is SPARC (secreted protein, acidic, and rich in cysteine) or osteonectin gene (chromosomal location 5q31.3-q32). SPARC is a matricellular protein that is present in the human intervertebral disc. SPARC levels decrease with aging and degeneration. Gruber et al. (2005) found that targeted deletion of SPARC in the mice led to accelerated LDD and herniations. The same authors found decreased presence of SPARC in disc cells of older human subjects with disc degeneration.[56] Our literature search did not uncover any studies confirming a direct association of the SPARC gene with IDD in humans.

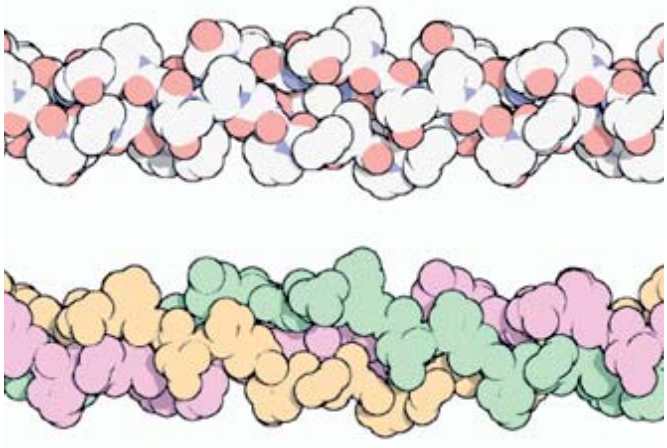

Figure 6. Two representations of a collagen helix.
Courtesy of David S. Goodsell and the RCSB PDB

Gene-gene and gene-environmental interactions. Simple linear models may fail to grasp the complexity of the real world. Unraveling the contribution of genes and environment in diseases of multifactorial etiology is a challenging proposition.[57] For specific genes and some environmental factors, gene–gene interactions and gene–environment interactions may exist. Gene-environment interaction can be defined as the effect of a gene on disease risk persons with different environmental exposures.[58] For example, Solovieva et al.[37] presented evidence suggesting that the effect of weight on lumbar disc degeneration is modified by COL9A3 gene polymorphisms in Finnish men. They found that COL9A3 gene polymorphisms and persistent obesity acted synergistically to increase the risk of dark nucleus pulposus, posterior disc bulge, decreased disc height, and multilevel posterior disc bulges. From 45% to 71% of disc degeneration among persistently obese individuals with the Trp3 allele could be attributed to the synergism of these two factors. Another example of gene–environment interaction in Solovieva's et al.[41] study suggested that the IL-1 gene cluster polymorphisms modified the effect of occupation on disc bulges and joint occurrence of degenerative changes. The negative effect of physical workload on IDD for carpenters was exaggerated by the presence of a minor allele of the polymorphism in all studied genes. For machine drivers, the effect of occupational load on bulges was modified only by the presence of the IL-1aT889 allele. In another study, the same authors provided evidence for gene-gene interaction.[38] As mentioned before, the association between COL9A2, COL9A3 and IL1 gene cluster polymorphisms and lumbar disc degeneration has been reported. Multivariate logistic regression analysis controlling for occupation and body mass index showed that the presence of the COL9A3 in the absence of the IL-1ß-T(3954) allele increased the risk of dark nucleus pulposus (OR 7.0, 95% CI: 1.3-38.8) and joint occurrence of degenerative changes (OR 8.0, 95% CI: 1.4-44.7). There was no effect of the COL9A3 on disc degeneration in the presence of the

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IL-1ß-T(3954) allele. The results suggest that the effect of the COL9A3 gene polymorphism on IDD might be modified by the IL-1 ß gene polymorphism.

Conclusions

Research has demonstrated the existence of familial predisposition to IDD. After adjustment for age, sex, BMI and bone mineral density[26] or for age, weight, height, smoking, occupational manual work, and exercise,[23] heritability estimates for IDD are very high and statistically significant (H= 0.73-0.75) and almost similar in the lumbar and cervical spine (0.74 and 0.73 respectively).[23] However, familial aggregation explained 61% of the total variance in summary LDD scores of the T12-L4 region but only 34% in the L4-L5 and L5-S1 region, in Battie's et al.[25] twins study. In addition, only 43% of IDD variance in the lower lumbar region can be explained by age, physical loading exposure and familial aggregation. From the aforementioned studies, we can state that heritability explains 34-75% of IDD variance, depending on the population studied and the level of intervertebral disc. Additional population based studies are required to confirm the heritability impact on IDD. Segregation analysis showed that the mode of inheritance is complex, with multiple factors and multiple genes likely involved in intergenerational transmission.[27]

A number of genes have been associated with IDD in humans, including genes coding for collagen I, collagen IX (COL9A2 and COL9A3), collagen XI (COL11A2), IL-1, IL-6, aggrecan, VDR, MMP-3, and CILP. Gene–gene interactions, gene–environment, and gene-age interactions may exist for specific genes and some environmental factors. Candidate-gene association studies have limitations in detecting the genetic basis of the disease because this approach relies on having predicted the correct genes on the basis of biological hypothesis or the location of the known linkage regions. The genome-wide association approach has no assumptions of the location of the causal variants and represents an unbiased yet fairly comprehensive approach even in the absence of knowledge of the function or location of the causal genes.[59] Additional studies, including linkage analyses and whole genome scan studies in different populations are required to improve our understanding of the influence of aforementioned genes on IDD and to identify novel genes.

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List of abbreviations used
CI - confidence interval
DZ – dizygotic
IDD - inervertebral disc degeneration
LBP - low back pain
LDD - lumbar disc degeneration
MRI - magnetic resonance imaging
MZ – monozygotic

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Mesenchymal Stem Cells

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Stem cell therapy has recently gained significant media attention for its potential for regeneration of nearly every organ in the human body, and has shown promise in the regeneration of many types of cells, from the myocytes of the heart[1] to the keratinocytes of the skin.[2] The human nervous system has remained an enigma to those who seek to repair damage caused by neoplastic growth or physical trauma. The father of neuroscience, Santiago Ramon y Cajal, once remarked about the potential for regeneration in this incredibly complex organ of the human body, "Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centers, the nerve paths are something fixed, ended, immutable. Everything may die, nothing may be regenerated."[3] The discovery that the human brain contained specific centers where new neurons grew and sprouted new connections within the brain drastically changed the concept of the human nervous system as rigid and fixed into its neonatal form. The discovery that the adult human brain contained stem cells which help to replenish neurons, the basic foundation of the human brain and spinal cord, opened up new avenues for the potential of regenerating the human nervous system.

Fetal Neural Stem Cells

Fetal neural stem cells were a likely initial candidate for basic research into applicability of manipulating normal human cells to regenerate the damaged nervous system. These cells are pluripotent, with the potential to differentiate into not only the neurons which, as aforementioned, serve as the basis for memory and function, but also the glial cells.[4] The latter are essential for both the survival of human neurons and the maintenance of synapses where information traverses from one neuron to another, forming memory and translating into actions. Additionally, these cells have a strong migratory capacity and have shown to be able to travel across the corpus callosum and into the contralateral hemisphere when injected into mice forebrains.[5] This incredible migratory ability was a very appealing aspect of fetal neural stem cells, because they could be genetically programmed to migrate long distances to sites of nervous tissue damage. However, the use of fetal neural stem cells presented significant ethical and practical problems. Unfortunately, the yield of these fetal neural tissue samples into therapeutic treatments is very low. Large numbers of fetal neural tissue samples need to be harvested to help grow just a few flasks of these precious neural stem cells, which may only be useful for a single patient. Additionally, the susceptibility of these cells to rejection by the immune system of the host presents a significant problem, as is also seen in the field of organ transplant therapy, where a high degree of rejection is likely even with a moderately compatible Human Leukocyte Antigens (HLA) match.[6] Thus, an ideal source of stem cells for the regeneration of the nervous system would be one where a large number of cells with HLA markers compatible with the recipient are present.

The Regenerative Potential of Mesenchymal Stem Cells in the Nervous system

Human mesenchymal stem cells (hMSCs) (Figure 1) have shown significant potential to circumvent the problems posed by the use of human fetal Stem Cells. These cells can be isolated from normal, healthy adults from two sources:

1. Simple bone marrow aspirate (identical to the procedure currently used for bone marrow donation).[7]

2. Fat aspirate from healthy human adults (similar to the liposuction procedure common in many plastic surgery clinics).[8]

The harvesting and subsequent culturing of these two sources yield a significant amount of human mesenchymal stem cells. Many have described very similar properties of these cells, despite being harvested from two different sources.[9]

These cells have a long list of properties which make them ideal for the use in regeneration of the human nervous system. They can be collected from normal, healthy adults[7] and be expanded in vitro for

reinfusion back into the donor. This circumvents the obvious ethical issues of isolating a large number of fetal tissues for potential use in only a few patients. Additionally, these cells can be isolated from the host as well, circumventing any issues with incompatibility and rejection which has been a problem for a large proportion of transplant patients.

Additionally, previous groups have established that unmodified mesenchymal stem cells can develop into various mesodermal cell types, including adipocytes, osteoclasts, chondrocytes, and myocytes.[10] More importantly, a postdoctoral member of our laboratory (E. Anghileri) has shown that murine mesenchymal stem cells harvested from fat tissue can differentiate into neuron-like cells.[11] Namely, she has found that when these cells are grown in specific media to induce the neuronal differentiation of these cells, they appear to morphologically resemble neurons, with an elongated shape and protrusion of two or three cellular processes.[11]

Additionally, these cells have a cell surface expression pattern which resembles adult neurons, with nestin and neuronal molecules (including GABA receptor and tyroxine hydroxylase), but not glial phenotypic markers.[11] Finally, these cells have electrophysiological evidence of early neuronal differentiation, showing negative membrane potential (-60 mV), delayed rectifier potassium currents and TTX-sensitive sodium currents.[11] This marks the important discovery that these cells exhibit multipotent behavior and convert into neuronal cells with the ability to transmit information through electrophysiological signals. With a better understanding of how to manipulate these cells into a specified fate, which is now actively being looked at in our laboratory, these cells can be used for the regeneration of damaged neurons seen in not only intracranial diseases, but also spinal diseases with the potential to regenerate severed neurons.

The Potential of Mesenchymal Stem Cells as a Treatment Modality Against Gliomas

Intramedullary spinal cord tumors account for approximately 2% of adult and 10% of pediatric central nervous system neoplasms. In adults, approximately 85-90% of these tumors are gliomas, and usually have a grim prognosis for patients. Mesenchymal

Figure 1. GFP Labeled human Mesenchymal Stem Cells

stem cells have been shown by several groups to locate and surround gliomas in animal models[12,13], and can serve as vehicles to deliver various agents to tumors including oncolytic viruses[10] and proteins with therapeutic efficacy against tumors.[14] Mesenchymal stem cells are attractive because they are abundantly available in the bone marrow,[15] can migrate long distances within the central nervous system parenchyma,[16] and can specifically locate CNS tumors. One potential use for these cells is to employ them to augment the body's innate immune system response against brain tumors. Gliomas have the ability to cause local immunosupression.[17] Thus, one idea has been to use the immunostimulatory cytokine IL-12 to inhibit tumor progression by causing an inflammatory response.[18,19] Our brain tumor research group has previously characterized the ability of the immunostimulatory cytokine IL-12 to inhibit the growth of human gliomas by enhancing the endogenous immune system.[19] Our research laboratory has been studying whether genetic modification of hMSCs to secrete human IL-12 may have therapeutic efficacy by locally delivering IL-12 to the site of human gliomas. This will, in theory, serve to augment the body's immune system against the tumor. We hypothesize that IL12-hMSCs are capable of (i) selectively migrating to the glioma and (ii) suppressing tumor growth by recruiting the host immune system to locally destroy the malignant tumor (Figure 2).

Mesenchymal Stem Cells

However, these proposed effects of hMSCs on tumors are controversial. Some studies have shown that tumor cells can form gap junctions with MSCs.

These gap junction connections are believed to be involved in the induction of hMSCs to become tumorigenic and paradoxically enhance the growth of the tumor by differentiating into tumor stromal cells.[20-22] Conversely, studies have shown that transplantation of genetically modified hMSCs increases the long term survival in several animal models[13,14,16]. Nevertheless, it remains unknown what happens to hMSCs upon locating gliomas in vivo. We are currently actively studying the fate of IL12-hMSCs after interacting with human gliomas both in vitro and in vivo conditions. These experiments may reveal necessary information regarding the therapeutic potential and underlying anti- or pro-tumor properties of genetically-modified hMSCs specifically.

Conclusions and Future Directions

Our research has the potential to radically advance the current treatment of intraspinal injuries and intramedullary spinal tumors using mesenchymal stem cells. MSCs represent a readily accessible, pluripotent source of stem cells which can be modified to generate adult neurons to treat severed neuronal connections from axonal injury. In addition to their regenerative potential, mesenchymal stem cells are also being studied by our laboratory as a delivery vehicle for a proinflammatory cytokine against gliomas. At present, surgery followed by radiation and chemotherapy is the gold standard in the treatment of brain tumors, and the median survival for patients with glioblastoma multiforme is only 14.6 months. By using genetically engineered human mesenchymal stem cells to deliver cytokines locally to tumors in the brain or spinal cord, a new medical treatment strategy will be implemented

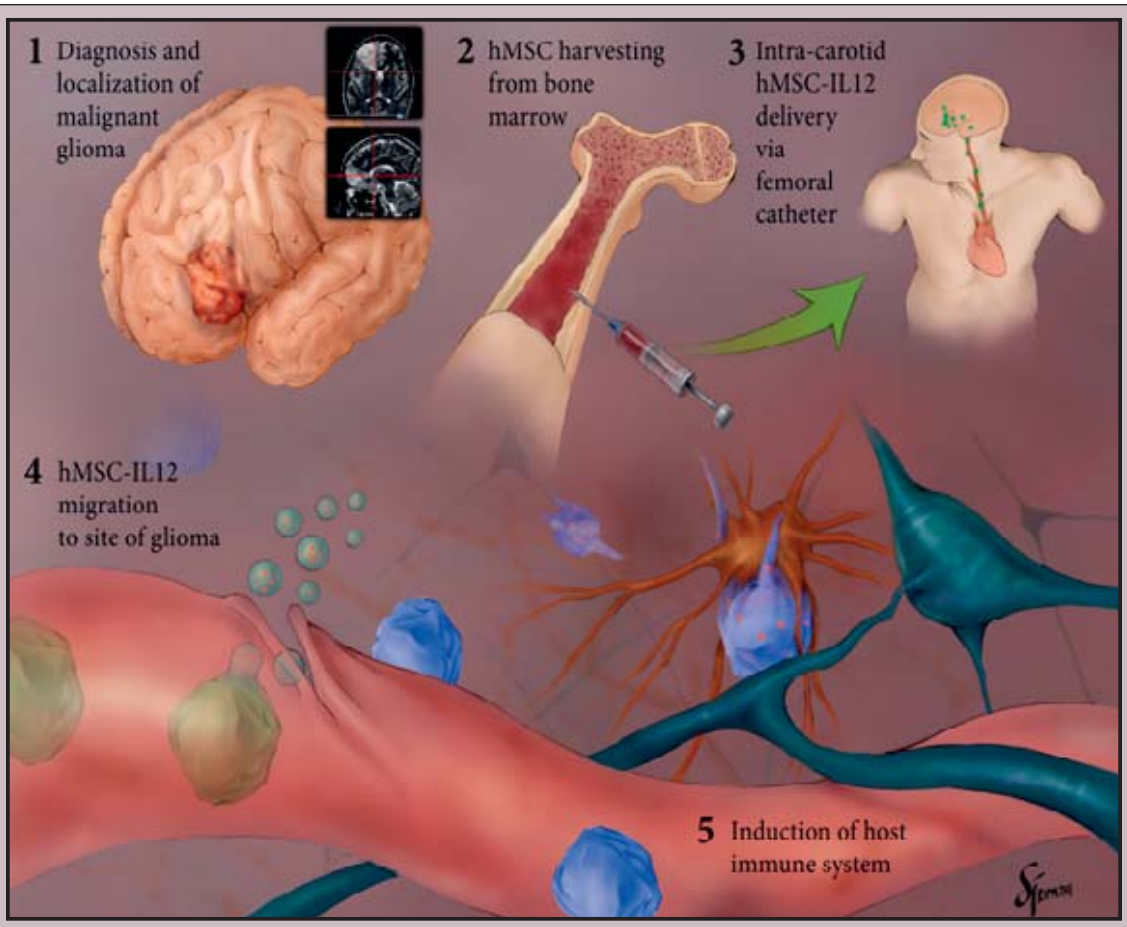

Figure 2. Potential Clinical Application of genetically engineered IL12-hMSCs.

that will take into consideration the innate ability of our own bodies to fight malignancies. We have the ability to recapitulate human disease in an animal model, which will allow us to not only to accurately track the true therapeutic capability of genetically modified hMSCs against human brain tumors, but also to understand the progression of this disease and its interaction with the immune system. We predict that we will be able to show that hMSCs have the ability to migrate to human stem cell derived gliomas, produce IL-12 at that site, and induce an inflammatory reaction which will ultimately aid in the regression of the tumor and impart increased survivability. Our proposal will be the strongest case yet for the use of hMSCs in the treatment of real brain tumor patients since we will be the first group to understand the efficacy of hMSCs against human gliomas, using a human immune system. We are optimistic that we will be able to bring the use of hMSCs to clinical trials for patients.

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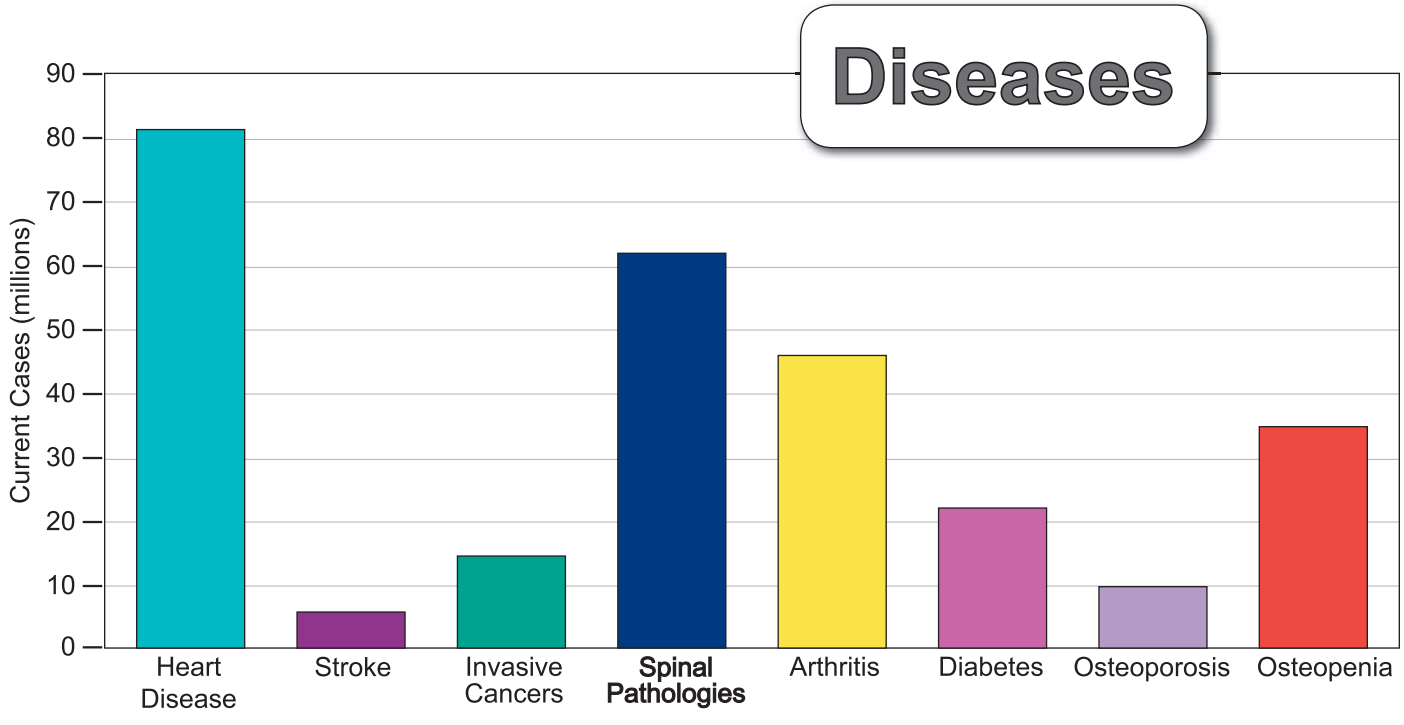
According to the National Institutes of Health

- At some point, neck or back pain affects an estimated 9 out of 10 people. It is one of our society's most common medical problems.
- The first attack of neck or low back pain typically occurs between the ages of 30 and 40. Spinal pain becomes more common with age.
- With symptoms ranging from a dull ache to absolute agony, back pain can put your life on hold.
- In fact, it is second only to the common cold in causing missed workdays for adults under age 45.
- Office visits for low back pain: 25 million per year
- Medical admissions for low back pain: 325,000 per year



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Heart Disease- http://www.americanheart.org/presenter.jhtml?identifi er=4478
Arthritis- http://www.cdc.gov/nchs/fastats/arthrits.htm
Diabetes- http://www.diabetes.org/about-diabetes.jsp
Osteoporosis- http://www.nof.org/osteoporosis/diseasefacts.htm
Cancer- National Cancer Institute 1975-2005 statistics.

Neck and Back Pain Affects Millions

The Spinal Research Foundation has made remarkable progress in scientific research associated with neck and back pain. Located in Reston, Virginia, the Foundation collects data relative to patients' treatment and outcomes and has embarked on projects designed to better understand the biochemistry of neuropathic pain and develop new drug and surgical regimens to address it. The Foundation continues to expand its research efforts, partnering with other research institutions to further the advancement of spine related research. The Spinal Research Foundation has been involved in numerous studies:

- ***The use of novel perioperative drug therapy to improve surgical outcomes.***
- ***The evaluation of medical devices for the relief of back pain.***
- ***The evaluation of analgesic drug regimens.***
- ***The development of non-operative techniques to resolve disabling neck and back pain.***
- ***Investigating the use of BMP (Bone Morphogenetic Protein) in minimally invasive spinal surgery to minimize post-operative pain and dysfunction.***
- ***The development of cervical and lumbar disc replacement technologies.***
- ***The development of disc regeneration technology through the use of stem cells derived from the bone marrow.***
- ***The investigation of lactic acid polymers to prevent fibroblast in-growth in surgical wounds.***
- ***A nation-wide multi-center prospective spine treatment outcomes study.***

The Spinal Research Foundation is an international non-profit organization dedicated to improving spinal health care through research and education. The Foundation collaborates with spinal research centers of excellence around the world to prove the success of traditional approaches, as well as develop new techniques and technologies. These results are shared with both the medical profession and the general public to improve the overall quality and understanding of optimal spinal health care.

More than 85% of the population will suffer from severe neck and/or low back pain during their lifetime. Eight percent of these people develop chronic pain, which means that at any given time, 25 million people in the United States are directly affected by this condition and many more indirectly. Techniques to cure, manage, and prevent this limiting and disabling condition need to be developed. Educating the public, health care providers, and insurance providers is the first step in advancing spinal health care.

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