Postmortem findings in the Coffin-Lowry Syndrome

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The Coffin-Lowry Syndrome (CLS) is a congenital disorder that can be recognized by retarded growth and development, the characteristic appearance of the face and hands, and often by the typical deformities of the back and chest; there are many other anomalies. The history of the syndrome is reviewed, noting the x-linked semidominant pattern of inheritance, and two autopsies are presented and compared with the three autopsy reports that have been published previously. The five young patients died at ages between 18 to 28 years of advancing pneumonia, aspiration of food into the trachea, or postoperative complications. There were lesions or abnormalities in the heart, brain, lungs, liver, skeleton, kidneys, intestines, and other organs. Molecular geneticists have located the CLS gene or Rsk-2 gene at Xp22.2 and demonstrated that it works by influencing the activation of other genes. The "monopolygenic" pattern may help to explain the large number of seemingly unrelated abnormalities that make up this syndrome. ***Genet Med* 2003:5(3):187–193.**

Key Words: *Coffin-Lowry Syndrome, CLS, autopsies, gene locus Xp22.2, enzyme Rsk-2*

In 1966 Coffin, Siris, and Wegienka[1] described a syndrome in two unrelated boys that has become known as the Coffin-Lowry Syndrome (CLS). Our examination of both boys showed developmental retardation, short stature, plump, soft hands with lax, extensible joints and tapered fingers, and a distinctive facial appearance, with wide-set, down-slanted palpebral fissures, epicanthi, ptosis of the upper eyelids, flat maxillae, thick nasal septa, anteverted nostrils, and prominent forehead, brows, ears, and lips. Teeth were few and misaligned. Muscles were weak and hypotonic. The skin was easily stretched. Ligaments were loose, and feet were flat. The gait was slow, awkward, and shuffling. Each boy had kyphosis, a short bifid sternum, and pectus carinatum or excavatum. Both boys fell frequently. One boy had a heart murmur. X-ray studies showed a thick calvarium, small paranasal sinuses, delayed bone age, narrow-necked or "drumstick" terminal phalanges of the fingers, and a frayed and beaked anterior contour of several vertebral bodies. Respiratory infections were frequent. Intelligence quotients (IQ) varied from 54 to 20, and, like other aspects of the syndrome, seemed to grow worse with age. The mothers of both boys, and the sister and half-sister of one of them, had similar but less distinct anomalies and less disability.

Soon after these first cases were published, we received communications from Italy, France, and Australia describing individuals and families with the same syndrome.[2–4] In addition, we evaluated a family[5] in which seven persons were affected in four generations, with transmission only from mother to child and with wide variation among females; some were severely disabled and others were unimpaired.

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DOI: 10.1097/01.GIM.0000067991.73943.4F

The second published report of the CLS was by Martinelli and Campailla in 1969[2] that described a boy whose parents and siblings showed no evidence of the syndrome. In 1970, Siris and Coffin[6] published the Coffin-Siris Syndrome, a recognizable inborn error of development that is not the same as CLS. However, shared authorship has caused confusion between these names,[7] and an old dictionary even cited the two syndromes as the same disorder with two different names.

The next 5 years produced additional reports of this syndrome. In 1971, Lowry et al.[8] described a fourth family with CLS, and Coffin and Siris[5] presented a fifth large family. In 1972, Carpentier[3] reviewed two familial cases and three sporadic cases, and Procopis and Turner[4] described a large Australian family showing probable x-linked dominant inheritance with variable penetrance. In 1973, a family was described by Jammes et al.[9] In 1974, Hussels[10] described a boy whose mother and sister were mildly affected. In 1975, De Marco[11] presented a sporadic case. In 1975, Temtamy et al.[12,13] presented three families. To prevent confusion, Temtamy suggested the eponym Coffin-Lowry Syndrome, which has become the standard term. In 1976, Smith[14] reviewed the syndrome and accepted it as genuine.

Additional publications since 1976 are listed in the bibliography.[15–54] They add several clinical and pathologic findings as probable features of the syndrome: thickened forearms,[15–17] delayed closure of the anterior fontanel,[8,9,18–22] and a conspicuous longitudinal furrow or groove in the dorsum of the tongue.[7,9,12,23–25] Dental anomalies have been described[7,11,17,19,23–34] and include congenital absence of some teeth, delayed eruption, enamel hypoplasia, caries, early tooth loss, deformities, unusual sizes, malposition, and misalignments.

Sensorineural hearing impairment can appear in childhood:[16,26,27,31,35–37] slow conduction of the nerve impulse has been noted,[38] but normal conduction has also been reported.[4,9] Epilepsy does occur,[1,8,17,23,25,29,39–41] although the frequent

falls or "drop attacks"[42–46] appear to be cataplexy or hyperexplexia (abrupt loss of muscle tone when the individual is startled). One patient ceased having attacks after surgery for scoliosis.[45] Psychoses have been mentioned[9,28,35,37,40] and a possible obsessive-compulsive tendency as well.[30,72]

Central nervous system changes are reported, including agenesis of the corpus callosum[21,41,47] and calcification of the falx cerebri.[23] A variety of cardiovascular abnormalities are reported, including murmur,[1] increased impulse,[4] and congenital heart disease.[9] mitral prolapse or insufficiency,[7,12,17,18,48] patent ductus arteriosus,[21] and tricuspid insufficiency with decompensation and right ventricular hypertrophy.[49] Inguinal hernias,[1,7,12,17,27,35] umbilical hernia,[3] rectal prolapse,[1] and uterine prolapse[7,12] have been reported. Many of these features have been listed and tabulated,[17,18,23,29] and they are summarized in the standard texts.[50,51] Visual problems and life expectancy have not drawn much attention.

Early searches for a metabolic disorder gave mixed results. In the first two patients,[1] we found a lack of subcutaneous elastic fibers, although later observers have reported normal elastic fibers.[4,7,12,15,23] Others have found radiographically detectable calcification of the elastic fibers of the ligamenta flava.[55–57]

Investigation of connective tissue has provided few common features. Vacuoles in skin fibroblasts,[4] glycolipid-like lysosomal granules and vacuoles in cultured skin fibroblasts,[10,12] and cytoplasmic granules in cultured cartilage cells[58] have been observed, as have lipid droplets, which are probably normal, in fibroblasts and endothelial cells.[18] Abnormal proteodermatan sulfate in cultures of skin fibroblasts from three patients,[59] an accumulation of hyaluronate in cultured skin fibroblasts and the culture medium,[55] and hypoprolinemia as an incidental finding in one family[32] are reported here.

In 1987, Machin et al.[60] presented the postmortem findings from two young adults with CLS (a brother and sister whose clinical course had been described by Lowry et al.[8]) In 1988, there was a brief note about a third autopsy.[25] The three autopsies are summarized in Table 2. These autopsy reports redirected attention to the first two boys[1] described with this syndrome in 1966. Their medical records were retrieved, giving additional clinical information, and the results of both postmortem examinations, which are presented now.

CASE A

Case A has been previously described.[1] The boy's mother was short in stature and had severe headaches but was not retarded in development. Her face and hands were characteristic of the syndrome but less affected than those of her son. Other relatives seemed healthy and unimpaired. This boy was born normally after a normal pregnancy. Development was slow in infancy, rickets were suspected, and his face appeared unusual (Fig. 1). Speech was severely delayed. Because of insomnia and restless wandering, he was admitted at age 8 to an institution for the mentally retarded. He achieved an IQ of 54 at age 10 and 25 at age 18. He had the habit of eating large amounts rapidly. There were frequent falls, frequent respiratory infections, and one rectal prolapse. He was treated with phenytoin because of an abnormal electroencephalogram and with iodochlorhydroxyquin to prevent amebiasis.

Physical examination at age 18 showed small size and quite a small head, cheerful behavior, some ability to see and hear, minimal speech in unrecognizable words and short sentences, stooped posture with flat feet, bent knees, head tilted to the right, a gait that was slow and shuffling and wide based, loose, stretchable skin with many scars, weak hypotonic muscles, lax

Table 2
Previous reports of postmortem findings in coffin-Lowry Syndrome

	Patient 1, female age 28[60]	Patient 2, male age 22[60]	Patient 3, male age 19[25]
Mode of death	Suspected asphyxia after lip operation	Renal and hepatic failure; urinary tract infection	Cardiac arrest during operation for scoliosis
General	Typical face, hands, stature; many scars	Typical face, hands, stature, back	Typical face, hands, stature, back
Brain	Mild ventricular dilation	Moderate ventricular dilation; simple and unusual gyral pattern; not neuronal abnormality	Not examined
Lungs	Emphysema, vascular congestion, thrombi, subpleural plaques; hemosiderosis as in cardiac failure	Emphysema, subpleural calci-ic plaques (history of cyanosis)	History of dyspnea and respiratory repercussions
Heart	No abnormality (history of cyanosis)	Mitral insufficiency, short chordae tendinae; endocardial fibrosis; right ventricular hypertrophy	Endocardial fibroelastosis; dilated left ventricle
Intestine	Jejunal diverticula, areas of myenteric degeneration and aganglionosis	Sigmoid diverticula, myenteric ganglion cells few and "ballooned"	No abnormalities noted
Liver	Normal; no microscopic evidence of disease	Nodular cirrhosis; hepatomegaly; narrow bile ducts	No abnormalities noted
Kidneys		Many small cortical cysts	No abnormalities noted
Skull		Thick calvarium	No abnormalities noted

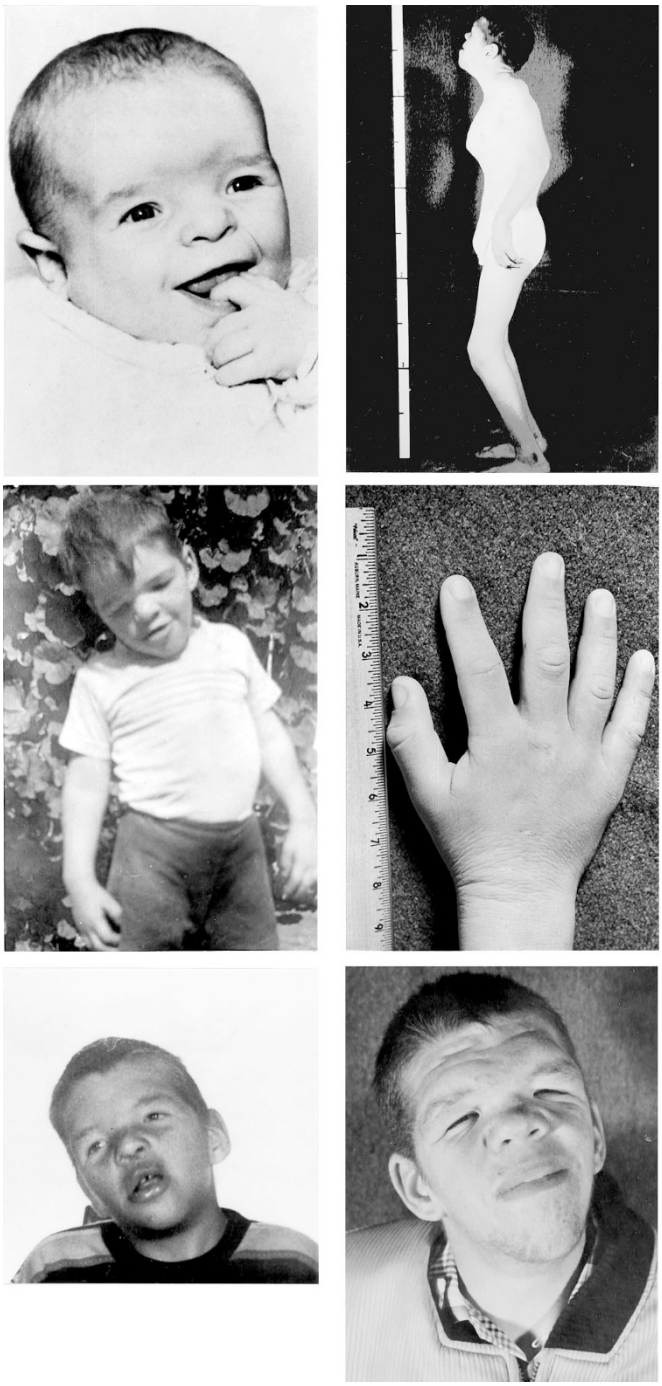

Fig. 1 Patient A: face at age 6 months, 4 years, 9 years, and 18 years; hand at 18 years; posture and profile at 19 years. Reproduced from Coffin et al.[1] (*Am J Dis Child* 1966;112: 205–213), copyrighted 1966, American Medical Association.

joints but minimal contractures at elbows and wrists, eyes that showed ptosis of the upper lids and some choroidal atrophy, thicker facial features (Fig. 1) with very bushy and prominent brows and also several scars and dull swollen nasal mucosa, few teeth that were badly misaligned and carious with some incisors pointed, low systolic heart murmur, chest asymmetric and anteriorly convex, stiff back with kyphoscoliosis, large plum-soft hands with loose extensible joint, and tapered fingers.

X-rays showed retarded bone age. Terminal phalanges of the fingers had wide or tufted tips, giving a collar-button or drumstick appearance. Frontal sinuses were large and maxillary sinuses small. Vertebral bodies T10 to L3 had frayed or notched anterior surfaces and an anterior prominence at L3.

Laboratory findings showed that blood was O+. Blood levels of growth hormone were normal. Chromosome appeared normal. Amino acid studies were normal. Biopsy of subcutaneous tissue showed very few elastic fibers, and biopsy of bone showed wavy epiphyseal line and misalignment of chondrocytes.

After these studies, the case was published, and the boy remained in institutional care. A hematoma of the scalp was aspirated several times. At the age of 18.5 years, he was treated for 6 weeks for pneumonia with left pulmonary abscess. Fever and weakness continued, and he died at age 18.75.

At autopsy, the lungs were adherent to the chest wall. There was acute passive congestion, and alveoli and tissues were infiltrated by neutrophilic leucocytes. The visceral pleura was thickened, and in the left interlobar fissure, there was an abscess 9 cm in diameter, with some hemorrhage around it. There was a 3 cm abscess within the right middle lobe and smaller abscesses in the left diaphragm. The pulmonary arterial walls were thick. The heart was dilated, and there was a 1.5 cm atrial septal defect. The wall of the left ventricle was thickened, and there were evidences of acute myocarditis, previous inflammatory disease, and diffuse fibrosis. The spleen was large and lobulated, with enlarged lymph follicles, congested blood vessels, amyloid around some of the arteries, and a thickened serosal capsule. Vacuoles and granules were seen in the hepatic cells (not Kupffer cells), and there were lymphocytes in the portal zones. The kidneys showed passive congestion, but the lower urinary tract was normal. The testes were small. The stomach was normal. Sections of intestinal wall showed a chronic inflammatory reaction but intact nerve plexi. The pancreas contained a small region of necrosis and scar tissue. The adrenal cortices were small and the cells were atypical in shape and staining. The pituitary gland was normal. The thyroid gland showed great variation in the size of the follicles, with follicle-free zones of scarring and lymphoid tissue. Samples of the bones from costochondral junctions showed irregular or disorderly arrangement of chondrocytes.

The external appearance of the 1290 g brain was normal, except that the gyral pattern in the cingulate area was complex. The corpus callosum was normal. The cerebellum was small and showed a tonsillar pressure cone. There was moderate patchy gliosis and loss of Purkinje cells. The anterior ventricles were slightly dilated, and the pineal body was cystic. Groups of corpora amylacea were seen in the ependyma and pia. In the cerebral cortex, there was patchy loss of neurons in the third and fifth laminae and a few anoxic neurons. Neurons in all portions of the brain showed sparse cytoplasmic granular material and possibly normal lipochrome.

CASE B

This boy's mother had severe headaches with emesis. She was moderately retarded in mental development and had the usual features of the CLS, including the tufted phalanges. The patient's sister and half sister also had the usual features. His birth was normal, but at the age of 1 week he was readmitted to the hospital for laryngeal dyspnea and began observation for slow development, pectus excavatum, and rapidly enlarging head. He did not learn to speak. At age 2, he had typical facies (Fig. 2).

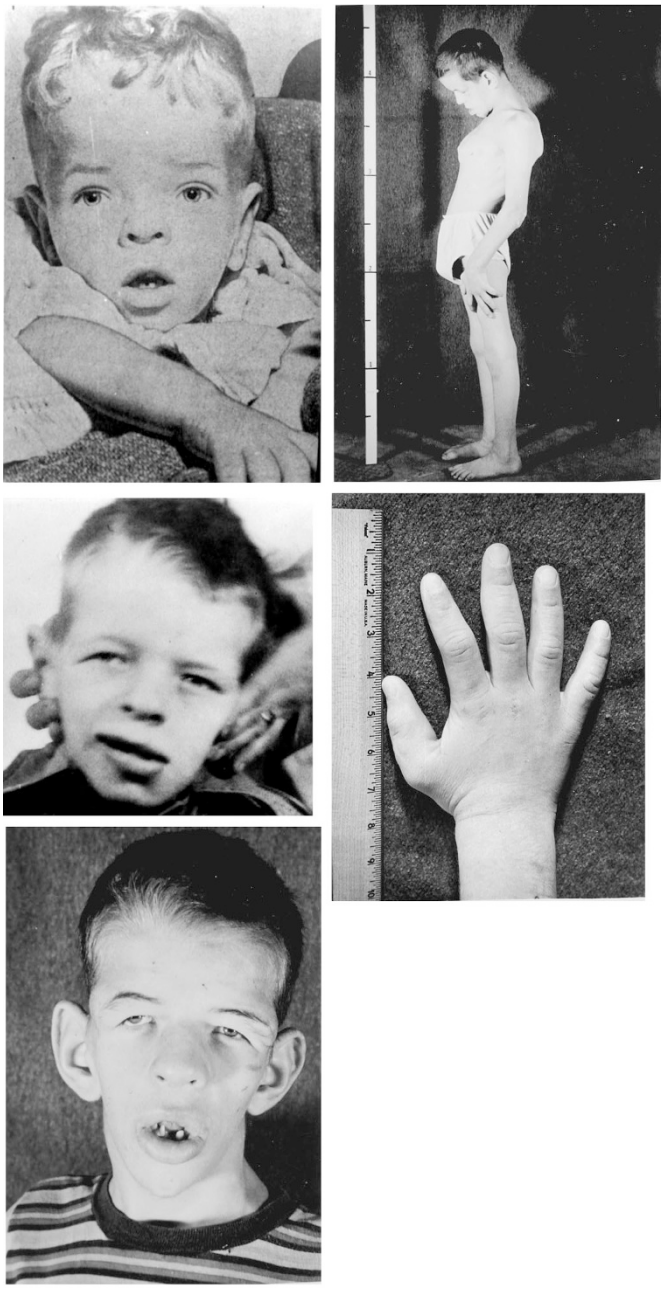

Fig. 2 Patient B: face at age 2 years, 9 years, and 15 years; hand at 15 years; posture and profile at 15 years. Reproduced from Coffin et al.[1] (*Am J Dis Child* 1966;112:205–213), copyrighted 1966, American Medical Association.

He was admitted to institutional care and achieved an IQ of 44 at age 2 and 20 at age 15. He was cheerful, friendly child, speechless but able to walk, see, and hear. He fell frequently and had frequent respiratory infections. He was treated with phenytoin and iodochlorhydroxyquin. His appearance changed through the years (Fig. 2). Because of loss of teeth, he took a very soft diet and ate large amounts rapidly. At age 14, he wandered about persistently shutting doors.

Physical examination at age 15.5 showed small size, large head, typical face and teeth, typical hands, pectus carinatum with kyphoscoliosis, lax skin, simian fold, hypothenar crease, palmar teeth, many scars, hypotonic weak muscles, lax joints, but flexion-contractures at wrists and elbows, flat feet with wide first toe-space, and clumsy gait.

X-rays showed retarded bone-age, thick calvarium, small paranasal sinuses, short, bifid, very prominent sternum, vertebral anomalies including midline defects in the neural arches T12 to S2, and anterosuperior notches in vertebral bodies T9 to S3 with beak-like anterior protrusions.

Laboratory tests gave many normal results: blood A+, chromosomes normal, amino-acid levels normal, tests for mucopolysaccharides negative, blood growth-hormone concentrations normal. Biopsy of bone showed irregular alignment of chondrocytes.

After these studies, his case was published,[1] and he remained contented and comfortable in the institution. At age 18.33 he was found lying on the floor apneic and moribund, and he died soon afterward.

At autopsy (Table 1), the trachea and main bronchi were completely obstructed, and the stomach and esophagus were dilated with food. There was widespread emphysema and fibrosis of the lungs and some foci of lymphocytes consistent with chronic pulmonary disease and previous episodes of pneumonia. The heart showed spotty subendocardial fibrosis, focal myocardial scars, and myocardial ischemia. The central veins of the hepatic lobules were distended, with cloudy swelling of hepatic cells but no granules. The splenic blood vessels were engorged. Fibrosis was found in the pancreas. The thyroid, pituitary, and adrenal glands were not remarkable. The kidneys showed distention of vessels and glomeruli. The urinary tract appeared normal, and the prostate was quite small (other organs were not described).

The brain weighed 1340 g. The meninges were thickened at the vertex, and the brain itself was very rounded, with a simplified gyral pattern except for small anomalous foci of microgyria. Minimal cerebellar coning was noted. The corpus callosum was not remarkable. The cerebral cortex was thin, but the deep white matter was bulky, and the ventricles were small. The microscopic studies showed faulty cortical lamination and some ectopic neurons and immature fusiform neurons. Granulations were not mentioned, and there was no evidence of mucopolysaccharidosis. The autopsy diagnoses were asphyxia caused by aspiration of food, pulmonary emphysema and fibrosis with moderate chronic pneumonitis, multiple congenital anomalies, mental retardation, focal scars in the myocardium, and subendocardial fibroelastosis.

Table 1
Postmortem findings in the Coffin-Lowry Syndrome

	Patient A, male, age 18.8	Patient B, male, age 18
Mode of death	Pneumonia with large pulmonary abscess	Aspiration of food into trachea
General appearance	Typical face, hands, stature, back, chest, many scars	Typical face, hands, back, stature, chest, teeth, nose
Brain	Small, dilated ventricles, unusual pattern of gyri; "anoxic" neuronnins in defective lamination	Rounded, small ventricles, anomalous gyral pattern, "immature" neurons in faulty lamination; thin cortex; thick white matter and anterior meninges
Lungs	Bilateral bronchopneumonia, pleural scars and adhesions; abscesses; passive congestion of blood vessels	Emphysema; widespread fibrosis, chronic pneumonitis
Heart	Interatrial septal defect; cardiac dilation; thick left ventricular wall; myocardial fibrosis and inflammation; passive congestion of abdominal viscera	Myocardial ischemia and focal scarring; subendocardial fibrosis; passive congestion of abdominal viscera
Stomach	Normal	Stomach, esophagus, and trachea filled with soft food
Intestine	Chronic inflammation; intact plexi	Normal
Liver	Granules and vacuoles in hepatic cells	Cloudy swelling of hepatic cells
Pancreas	Small, some scarring	Fibrosis or scarring in some areas
Kidneys	Passive congestion of veins	Passive congestion of veins
Skull	Calvarium no thickened	Thickened calvarium
Bone	Irregular alignment of cells at epiphyses	

DISCUSSION

The history of the CLS is reviewed, and two autopsies are presented from the two first cases, which were published in 1966. The autopsy reports, summarized in Table 1, reiterate well-known features of the syndrome, including chronic lung disease and heart disease and two additional items of special interest: the irregularity of cell alignment at costochondral junctions, and, in one patient, the presence of granular deposits in hepatic cells and in a few cerebral neurons. Three autopsy reports had been published previously[25,60] and are summarized in Table 2.

A comparison of these five cases emphasizes the great variation from patient to patient and the wide assortment of organs and tissues involved. The causes of death were varied but showed some similarities, including aspiration of food and intolerance of surgical procedures. The four brains that were examined showed dilation of the ventricles (3 of 4 cases), unusual patterns of gyri (3 of 4), faulty cortical lamination (3 of 4), abnormal appearance of cortical neurons (2 of 4), and thickened white matter (1 of 4). Unexpectedly, the corpora callosa were normal. The lungs showed emphysema (3 of 5 cases), scarring (4 of 5), vascular congestion (2 of 5), chronic infection (2 of 5), and in one case, fatal acute superinfection. In one case, the lungs seemed normal. In the heart, endocardial fibrosis was found in four of five cases, whereas myocarditis, mitral valve disease, tricuspid insufficiency, and atrial septal defect were found in one each and evidence of dilation hypertrophy or failure in three. In the skeleton, thickened calvaria were found in two patients, confirming earlier x-ray findings. In one patient, microscopic examination of bone showed irregularity of epiphyseal lines. Two cases, sister and brother, had diverticulae of the intestine and deterioration of the myenteric plexi, whereas two other patients had normal intestines, and one had chronic inflammation but intact plexi. In the liver, nodular cirrhosis and narrow bile ducts were found in one patient, who died in hepatorenal failure. Granules and vacuoles were found in hepatic cells of another, and "cloudy swelling" in hepatic cells of a third. Other organs were also abnormal: pancreatic scarring was found in two patients, cortical cysts of the kidneys in one, and amyloid deposits in the spleen of one. Scarring and lymphocytosis of the thyroid stroma were found. These autopsy findings and clinical findings do not include all of the anomalies found in CLS and do not exclude coincidental anomalies. However, the great variation from patient to patient and the wide variety of seemingly unrelated lessons in scattered organs imply a complex pattern of causation. Genetic research, which has been reported since the 1980s, may help to explain this pattern.

Molecular genetic studies of CLS have been reviewed.[17,61] The gene for CLS has been located[40,62–65] on the short arm of the X chromosome at band xp22.2, and the gene product is the enzyme Ribosomal S6 kinase or Rsk2.[66] The gene works mainly by its influence on the activation of other genes, a pattern which could be called monopolygenic. In a healthy person, the normal enzyme Rsk2 cooperates with a growth factor to promote mitosis and activate genes.[67,68] In a person with CLS, there is an anomaly at one of the many mutation sites[61,66,72,77] along this gene locus that results in reduced activity of the enzyme[61,70] with consequent curtailed expression of its targeted genes.

Because of these discoveries, there are now in vitro diagnostic tests for this syndrome[17,68,72–75] and hopeful speculation

about future pharmacotherapy.[76] Also, the CLS, or Rsk2, gene has become a promising center of study of development. The gene and its enzyme appear to be associated with the action of insulin and the synthesis of glycogen,[76] with responsiveness to salicylates and susceptibility to heat shock[78] and with resistance to other stresses,[78] and it may prove to be essential to the survival of cells.[71] The most recent genetic studies are progressing by application of novel techniques, including the use of a knockout mouse that lacks a fully effective Rsk2 gene.[61,69,76,78] Already, these studies are beginning to explain the wide variety of clinical and pathologic features of the Syndrome, the great variation between one affected person and another, and the overlapping features share by one developmental syndrome and another. Eventually, these studies may identify the target genes and processes and link each important feature of CLS with its genetic causes.

In future case reports, environmental influences should be considered in addition to the genetic background. Especially important are the effects of institutional care on the development of children, the effects of repeated injury, and the side effects of chronic medication. It is possible that these first two patients received enough phenytoin to modify their abilities and facial appearance.

ADDENDUM

Since acceptance of this paper, surveys of CLS[79,80] showed only a minority of subjects to have a mutation of the RSK-2 gene. Moreover, one patient with CLS[81] had interstitial deletion of chromosome 10, another[82] had a duplication of 8p23, and another[83] case showed multiple translocations involving chromosomes 2, 3, 7, and 11. Determination of serum Rsk2 might help to explain such cases.

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