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Case 34-2016: A 17-Year-Old Boy with Myopia and Craniofacial and Skeletal Abnormalities

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PRESENTATION OF CASE

Dr. Angela E. Lin: A 17-year-old boy was referred to the medical genetics clinic of this hospital because of high myopia (i.e., severe nearsightedness) and craniofacial and other skeletal abnormalities.

As a child, the patient had had difficulty with articulation and had received speech therapy. When he was approximately 12 years of age, dental crowding and class III dentofacial growth pattern were noted (class I growth pattern indicates normal development, class II indicates protrusion of the maxilla, and class III indicates protrusion of the mandible), and between 12 and 16 years of age, the patient had orthodontic braces and a palate expander. After the braces were removed, difficulty eating and chewing reportedly worsened. Eight weeks before this evaluation, he was referred to the outpatient Oral and Maxillofacial Surgery department at this hospital.

Dr. Maria J. Troulis: On examination, the patient had frontal bossing, downward-slanted lateral canthi, symmetric hypoplasia of the midface and maxilla, and relative mandibular hyperplasia (i.e., hyperplasia of the mandible relative to the size of the maxilla and midface) (Fig. 1A and 1B). There was a negative overjet of more than 10 mm (i.e., the mandibular teeth extended more than 10 mm horizontally beyond the maxillary teeth), and the lower teeth were retroclined. The ears were in a normal position, but they protruded outward. He was referred to the medical genetics clinic for evaluation of a possible genetic cause of these and other skeletal abnormalities.

Dr. Lin: The patient was born at full term by vaginal delivery; his birth weight was 4.3 kg. A pectus excavatum was present at birth. His height was at the 80th percentile until he was 15 years of age, after which it plateaued at the 55th percentile. No developmental delays were noted during childhood.

An intermittent systolic heart murmur, which was graded 3 out of 6 (with 1 indicating a soft murmur and 6 indicating a loud murmur) had first been noted when the patient was 13 years of age. Evaluations by three cardiologists during the next 4 years revealed no cardiovascular symptoms or decreased capacity; electrocardiograms showed an indeterminate axis, and echocardiographic studies reportedly revealed a normal aortic-root size and no evidence of anomalous vasculature,

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N Engl J Med 2016;375:1879-90.
DOI: 10.1056/NEJMcpc1610096

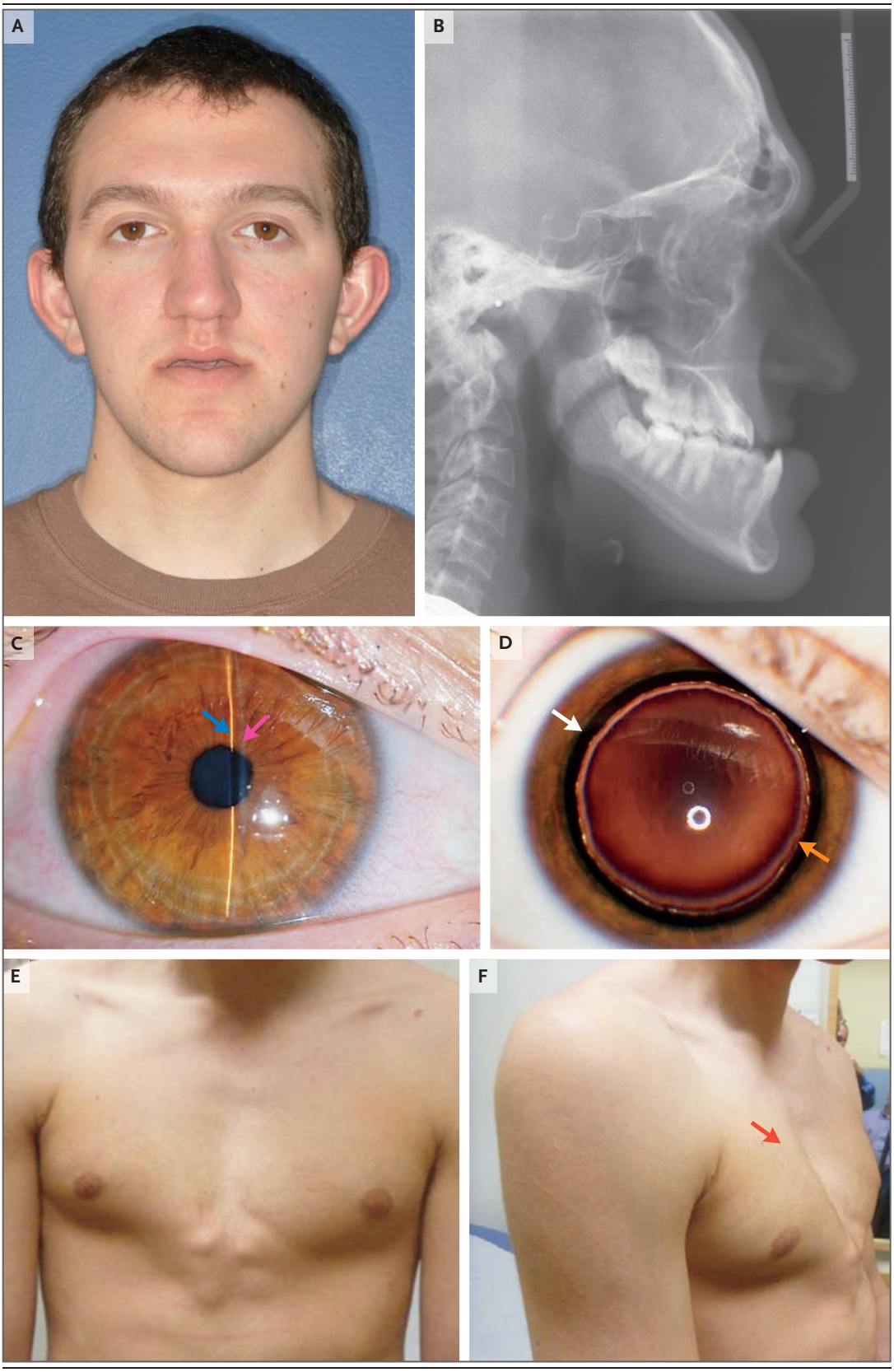

Figure 1 (facing page). Clinical Images.
A photograph (Panel A) shows mild frontal bossing, downward-slanted lateral canthi, low-set and protruding ears, and severe midface hypoplasia and maxillary retrognathia. A lateral cephalogram (Panel B) shows frontal bossing, severe midface retrognathia, negative overjet (with the lower teeth extending more than 10 mm horizontally beyond the upper teeth), and impacted 12-year molars. Findings were similar in both eyes. A second photograph shows the right eye before pharmacologic dilation (Panel C). The anterior chamber was determined to be shallow, because the vertical light beams on the iris (blue arrow) and cornea (pink arrow) were very close to each other. When the border of the right pupil (Panel D, white arrow) was enlarged by pharmacologic dilation, the entire lens perimeter (orange arrow) was seen, suggesting microspherophakia. There is a mixed chest-wall defect (Panel E) with a midsternal, funnel-shaped pectus excavatum defect and lower sternal protrusion with accompanying protrusion of parasternal cartilages (Panel F, red arrow).

atrial septal defect, valvular structural abnormalities, or findings suggestive of Marfan's syndrome. The murmur was thought to be turbulence related to the position of the heart in relation to the pectus deformity. On cardiogenetic examination performed at another hospital when the patient was 16 years of age, his weight was 69.2 kg, the height 177.8 cm, the arm span 188 cm, the ratio of arm span to height 1.06, and the ratio of upper to lower body segment 0.87. Pectus excavatum of the upper chest and pectus carinatum of the lower chest were seen, as were broad thumbs, with no evidence of joint hypermobility. Although there was insufficient evidence to diagnose Marfan's syndrome, a connective tissue abnormality was suspected. He was referred to a medical geneticist, but his family acknowledged that they were focused on the craniofacial evaluation.

Dr. Teresa C. Chen: When the patient was 13 years of age, a diagnosis of myopia was made, and eyeglasses were prescribed by his optometrist. Over the course of the next 4 years, examinations performed at the optometrist's office showed an increase of 12.75 diopters of myopia in the right eye and an increase of 11.00 diopters in the left eye. Nine months before this evaluation, his manifest refraction was reportedly –13.75 diopters in the right eye and –10.00 diopters in the left eye. Eight months before this evaluation, the patient was seen in the ophthalmology clinic at the Massachusetts Eye and Ear Infirmary.

On examination, his right eye refracted to a spherical equivalent of –14.50 diopters and his left eye refracted to a spherical equivalent of –11.00 diopters. Visual acuity was 20/20 in both eyes when the patient was wearing eyeglasses. The anterior chambers were shallow (Fig. 1C), and the angles were open on gonioscopy. The lenses were rounder and smaller than normal, and the lens perimeters and zonules were clearly visible in both eyes after dilation (Fig. 1D). The findings on ultrasound biomicroscopy were consistent with microspherophakia (small, spherically shaped lenses) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), with lens diameters of 8.41 mm in the right eye and 8.03 mm in the left eye (normal diameter, >9 mm). Lens thickness values were 4.97 mm in each eye. Axial lengths were 24.15 mm in the right eye and 23.91 mm in the left eye. Ultrasonography confirmed shallow anterior chambers, with anterior chamber depths of 2.20 mm in the right eye and 2.82 mm in the left eye (normal depth, >3.00 mm).

Dr. Lin: The patient had had no serious childhood illnesses. He had bilateral epididymal cysts that had been stable for many years, had undergone repair of urethral meatal stenosis, had had an impacted fracture of the wrist owing to a sports-related injury when he was 12 years of age, and had transient musculoskeletal back pain. He was not taking any medications. He had received all routine childhood immunizations and was allergic to melons. He lived with his parents and brother, and he did well in school. He had never used tobacco, alcohol, or illicit drugs.

The patient's brother, who was 3 years older than the patient, had a deep asymmetric pectus excavatum and a history of sports-related injuries, including several ankle injuries and recurrent avulsion of a hip joint associated with kicking. He did not wear eyeglasses and had no unusual facial features except for a mild underbite. The patient's mother was of Irish and Italian ancestry, and his father was of Italian, Portuguese, Irish, and Scottish ancestry; there was no known consanguinity. His father and multiple paternal relatives had hypertension; his paternal grandfather had coronary artery disease, his grandmother had an endocrine brain tumor, his aunt had Crohn's disease, and an uncle had arthritis. His mother was healthy, his maternal grandmother had non-Hodgkin's lymphoma, and a

cousin had celiac disease. His mother, maternal grandmother, and aunt were 165 cm tall; his brother and maternal grandfather were 170 cm tall; and his father was 175 cm tall.

On examination, the blood pressure and pulse were normal. The weight was 66.3 kg (48th percentile), the height 177.5 cm (58th percentile), and the head circumference 58.5 cm (98th percentile). There was slight frontal bossing. The conjunctivae were clear, and the sclerae were white, without blue or gray hue. There was a mixed chest-wall defect, with funnel-shaped pectus excavatum and lower sternal protrusion with protrusion of parasternal cartilages (Fig. 1E and 1F). A harsh, grade 3 systolic murmur was heard at the upper sternal border, without systolic click or diastolic murmur. There was loss of the normal upper curvature of the spine, as well as scoliosis, with the scapula and rib cage on the right side higher than the left. The remainder of the examination was normal or unchanged from recent previous examinations. The patient had above-average intelligence and was reserved. He asked thoughtful questions and consented to the proposed evaluations.

Dr. Sjirk J. Westra: Radiographs of the skeleton, including hands and feet, showed straightening of the normal cervical lordosis, rotatory S-shaped dextroconvex thoracic scoliosis, and generalized osteoporosis, with biconcavity of the end plates of multiple vertebral bodies, also known as "fish" or "codfish" vertebrae (Fig. 2A).[1,2]

A dual-energy x-ray absorptiometry scan (Fig. 2B) revealed an abnormally low bone mineral density of 0.75 g per square centimeter averaged over vertebral bodies L1 through L4; when compared with age-matched controls, this value resulted in a z score of –2.7, which is indicative of osteoporosis.

Dr. Lin: The blood level of phosphorus was 4.7 mg per deciliter (reference range, 3.0 to 4.5), and the level of 25-hydroxyvitamin D was 19 ng per milliliter (desired level, >32). A complete blood count and blood levels of electrolytes, folic acid, vitamin B_{12}, calcium, glucose, total protein, albumin, and globulin were normal. Tests of renal function were also normal.

Additional diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

OPHTHALMOLOGY PERSPECTIVE

Dr. Chen: All discussants are aware of the diagnosis in this case. The patient had rapidly progressing myopia. A myopic eye usually has a deep anterior chamber, which is a fluid-filled cavity that is delimited anteriorly by the dome-shaped cornea and posteriorly by the lens–iris diaphragm. In contrast, our patient had shallow anterior chambers (Fig. 1C). In a normal eye, the lens is suspended by zonules, which are radial strings that connect the lens equator to the eye wall. Conditions in which the lens zonules are abnormal and easily broken (e.g., homocystinuria, Marfan's syndrome, Ehlers–Danlos syndrome, hyperlysinemia, and sulfite oxidase deficiency) can lead to lens subluxation, or ectopia lentis. Instead of inferior and nasal subluxation, which is typically seen in homocystinuria, our patient initially had progressive anterior displacement of the lens, which caused worsening myopia and shallow anterior chambers.[3-6]

Disruption or abnormal laxity of the lens zonules can also lead to the development of microspherophakia, a condition that can cause lenticular myopia, which is nearsightedness caused by an abnormally positioned lens or an abnormally shaped lens (in contrast with classic axial myopia, which is nearsightedness caused by an abnormally long eye or a long axial length). Microspherophakia was first noted clinically in this patient, when the entire perimeter of the lens was seen after pharmacologic dilation (Fig. 1D). Usually, the edge of the lens cannot be seen with a pharmacologically dilated pupil, because the lens diameter is normally larger than the dilated pupil and is hidden behind the iris (the colored part of the eye). Our clinical suspicion of microspherophakia was confirmed by ultrasonography (Fig. S1 in the Supplementary Appendix).

MEDICAL GENETICS PERSPECTIVE

Important Features of the Case

Dr. Lin: This patient had several striking physical features, including prognathism, complex pectus deformity, kyphoscoliosis, high myopia, ectopia

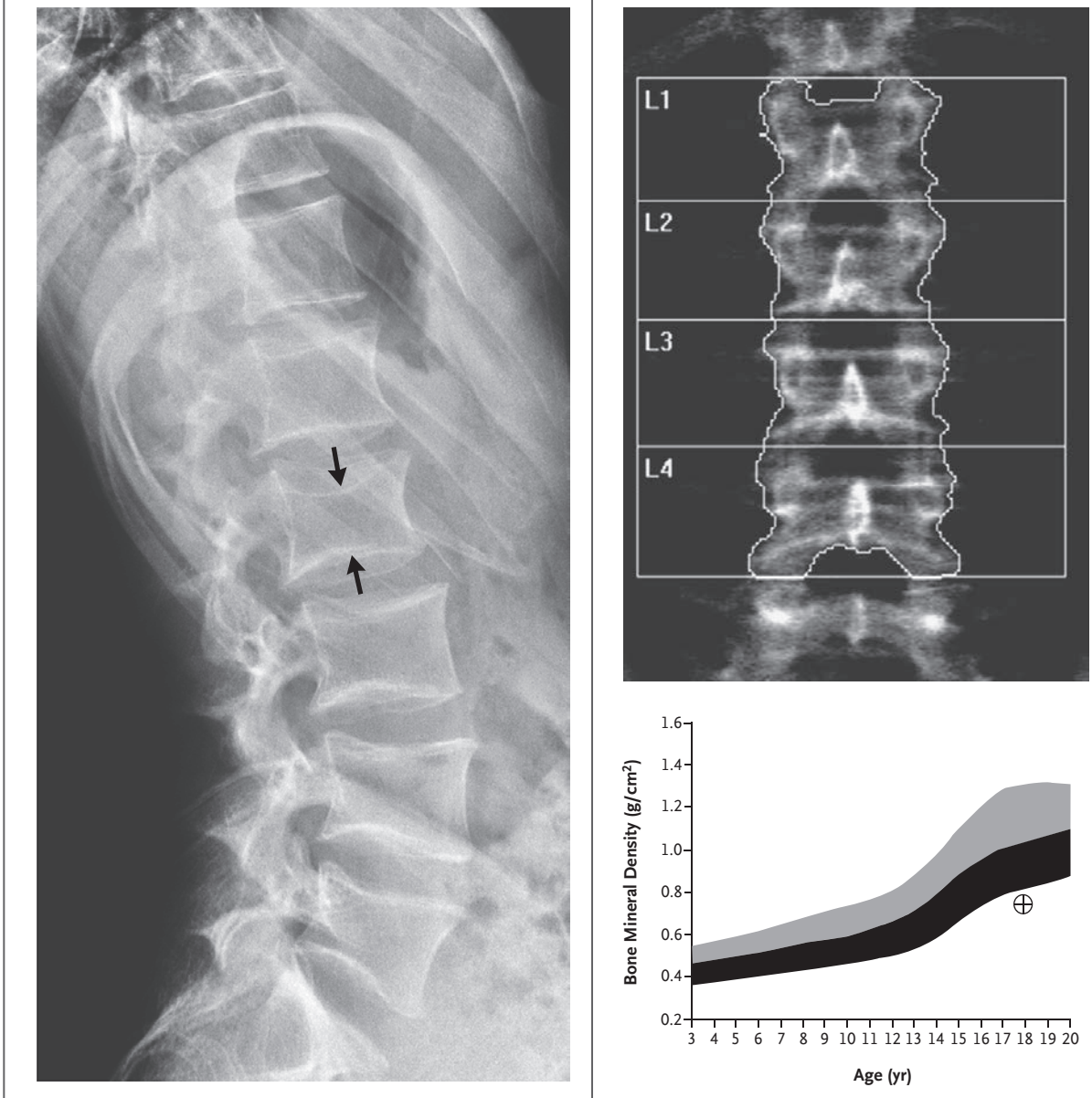

Figure 2. Imaging Studies.

Lateral view of the lumbar spine (Panel A) reveals concave superior and inferior end-plate depressions (identified by the arrows at L2) at multiple lumbar levels, giving rise to the appearance of "codfish" vertebrae. As measured with the use of dual-energy x-ray absorptiometry of the lumbar spine (Panel B), the total bone mineral density of the spine averaged over L1 through L4 was 0.75 g per square centimeter (indicated in the graph by the circle with a cross). This value was 2.7 SD below the expected normal value for the patient's age, corresponding to a z score of –2.7. The graph displays the age-related normal values with 95% confidence intervals. The gray area represents the median to the 95th percentile, and the black area represents the median to the 5th percentile. The intersection of the gray and black areas is the median. A z-score value lower than –2.0 indicates osteoporosis, and a value between –2.0 and 0 indicates osteopenia.

Table 1. Laboratory Data.

Variable	Reference Range, Age-Adjusted*	Patient	Patient's Brother
Homocysteine (μmol/liter)	0–14.2	237.0	16.8
Methionine (nmol/ml)	11–37	240	29
Methylmalonic acid (nmol/ml)	≤0.40	0.16	0.11
Methylcitrate (nmol/liter)	60–228	175	
Vitamin B_{12} (pg/ml)	>250	410	461
Folic acid (ng/ml)	3.1–17.5	10.4	
Hemoglobin (g/dl)	13.0–16.0	14.9	15.8
Hematocrit (%)	37.0–49.0	41.6	45.3
Mean corpuscular volume (fl)	78–98	86	97

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are age-adjusted for patients who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

lentis, and microspherophakia, as well as milder physical abnormalities, including a relatively large head, thin limbs, and mildly broad thumbs and halluces. He did not have tall stature, disproportionately long arms and legs, joint laxity, abnormal skin texture, or cardiac abnormalities such as mitral-valve prolapse and dilatation of the aorta. The change in his statural growth velocity appeared to be the result of a loss of vertebral height resulting from osteoporosis. Complicating the diagnosis was the family history of a brother with a more typical pectus excavatum and a milder form of prognathism; however, neither of these conditions progressed in the brother. The prognathism may be partly a familial characteristic in which the bone loss in the maxilla may exaggerate the disharmonic growth of the mandible.

These findings narrowed the possible diagnoses to only a few choices, two of which include features related to stature and lens dislocation that are very different from the features seen in this patient.

Marfan's Syndrome

I agree with the prior examiner who thought that Marfan's syndrome was an unlikely diagnosis, despite the striking chest-wall deformity, minimally increased arm span (ratio of arm span to height, 1.06), and high myopia. The clinical diagnostic criteria were not fulfilled, given the absence of aortic dilatation, striae distensae, and diffuse joint laxity, among other features.[7]

Weill–Marchesani Syndrome

The patient's microspherophakia and ectopia lentis could be associated with Weill–Marchesani syndrome, a distinctive connective-tissue disease that can be inherited in either an autosomal dominant or autosomal recessive form.[8,9] However, this syndrome includes short stature and brachydactyly, and cardiac anomalies are common, especially mitral-valve prolapse and aortic and pulmonary valve stenosis — features that are absent in our patient.

Homocystinuria

The patient's high myopia, microspherophakia, ectopia lentis, pectus deformity, "codfish" vertebrae, and kyphoscoliosis and the absence of aortic dilatation all suggested homocystinuria. We hypothesized that his brother might be similarly affected.

DR. ANGELA E. LIN'S DIAGNOSIS

Homocystinuria.

DIAGNOSTIC TESTING AND MANAGEMENT

DIAGNOSTIC TESTING

Dr. David A. Sweetser: We obtained a set of metabolic laboratory test results (Table 1). The results included a markedly elevated blood homocysteine level, at 237 μmol per liter (reference range, 0 to 14.2). This was supportive of, but not diagnostic for, homocystinuria.

Mild elevations in homocysteine levels can be associated with deficiencies of vitamin B_{12} or folate,[10] but these were normal in our patient. Low levels of either of these vitamins can cause macrocytic anemia, which he did not have (his hemoglobin level was 14.9 g per deciliter, the hematocrit level 41.6%, and the mean corpuscular volume, 86 fl [reference range, 78 to 98]).

A defect in vitamin B_{12} (cobalamin) processing affects the activity of two enzymes that require vitamin B_{12} as a cofactor: methylmalonyl–coenzyme A (CoA) mutase, which converts methylmalonyl–CoA to succinyl CoA, and me-

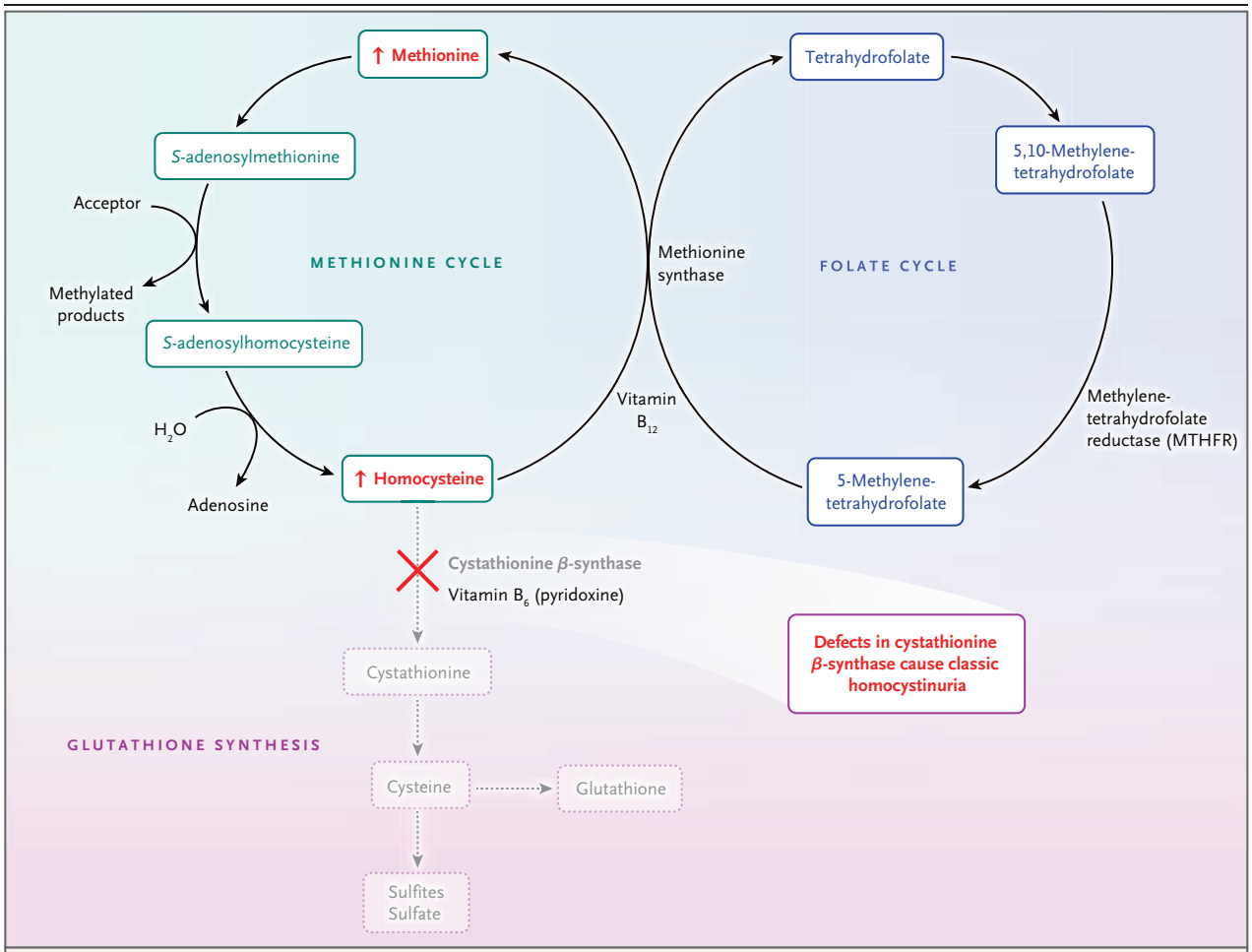

Figure 3. Schematic Representation of Homocysteine and Folate Metabolism.

Classic homocystinuria, which is caused by a deficiency in the enzyme cystathionine β-synthase, leads to elevated homocysteine and methionine levels, as well as to decreased cysteine levels and a decreased rate of glutathione synthesis. In some cases, the obstruction of the pathway can be partially overcome by supplementation with vitamin B_6, a cofactor for the enzyme.

thionine synthase, which converts homocysteine to methionine.[11] A low level of activity of these enzymes elevates the levels of methylmalonic acid and its derivatives, propionic acid and 2-methylcitrate, and causes elevation of homocysteine levels, with a decreased level of methionine.[12] In our patient, blood methylmalonic acid and methylcitrate levels were normal, whereas the methionine level was markedly elevated, at 240 nmol per milliliter (reference range, 11 to 37), which ruled out a defect in cobalamin metabolism (Table 1).

Elevations of homocysteine levels can arise from several defects in homocysteine and folate metabolism (Fig. 3). Deficiencies in 5,10-methylenetetrahydrofolate reductase lead to decreased conversion of homocysteine to methionine and elevated homocysteine levels, with normal or low levels of methionine. The finding of elevated homocysteine and methionine levels, as seen in our patient, is characteristic of defects in cystathionine β-synthase, which directly metabolizes homocysteine to cystathionine on the pathway to becoming cysteine and glutathione. This enzyme relies on the cofactor vitamin B_6 (pyridoxine). Defects in cystathionine β-synthase cause classic homocystinuria.[10] Thus, these findings in our patient supported the diagnosis of cystathionine β-synthase deficiency, or classic homocystinuria.

Genetic testing showed the presence of com-

pound heterozygosity for two known pathogenic mutations (p.Cys109Arg and p.Ala114Val) in the cystathionine β-synthase gene (*CBS*). The patient was also homozygous for the C677T polymorphism (p.Ala222Val) in the 5,10-methylenetetrahydrofolate reductase gene (*MTHFR*). The C677T polymorphism is present in a single copy in approximately 15 to 42% of various populations and in either a homozygous state (i.e., two copies) or a compound heterozygous state in combination with another common polymorphism (A1298C) in 11 to 20% of the general population.[13] However, the presence of dual polymorphisms causes, at most, only mild elevations in homocysteine levels, and this generally occurs only under specific conditions, such as when vitamin B_{12} or pyridoxine deficiencies are present.

The patient's brother had pectus excavatum and an underbite, which raises concern that he might also have homocystinuria. Results of his laboratory studies showed a mild elevation in the homocysteine level (16.8 μmol per liter), with normal levels of methionine, methylmalonic acid, and vitamin B_{12}. The results of his complete blood count were normal. He was heterozygous for a pathogenic mutation in *CBS* (p.Ala114Val). Since homocystinuria is a recessive condition, this mutation would not be expected to cause symptoms. He was also homozygous for the C667T mutation in *MTHFR*. The combination of these factors, in conjunction with environmental factors or diet, probably led to his mildly elevated homocysteine level. The result of a repeat laboratory test of his homocysteine level, performed 4 months after the first study, was normal, at 11.3 μmol per liter. We recommended that he take 1 mg of folate per day, and with the additional folate his subsequent homocysteine levels have remained normal.

CLINICAL MANIFESTATIONS OF HOMOCYSTINURIA

The clinical features of homocystinuria are variable and include ocular and skeletal manifestations. Ectopia lentis, as seen in this case, is a quite distinctive feature that can serve as a clue to the diagnosis. High myopia is also common and can precede the development of ectopia lentis. Microspherophakia is less common, and other ocular findings can include retinal detachments, optic atrophy, and cataracts.

Among the skeletal manifestations, osteoporosis — a prominent finding in our patient — is the most common. Elevated homocysteine levels affect the formation and cross-linking of collagen, which results in some structural bone loss. Levels of sulphated proteoglycans are also elevated in patients with homocystinuria.[14] Severe osteoporosis in a young patient should always suggest the possibility of homocystinuria. Our patient had classic skeletal changes, including "codfish" vertebrae and a pectus deformity. Wide metaphyses, a high arched palate, as well as other findings that are common in Marfan's syndrome, such as arachnodactyly and kyphosis, can be seen. The central nervous system is also commonly involved in homocystinuria, and developmental delay, psychosis, or psychiatric disturbances can be presenting symptoms; fortunately, these were not present in our patient. Seizures can be seen in about 20% of patients with homocystinuria.[12,15]

Our patient had not had a thrombotic episode or a cerebrovascular event, either of which is a very common initial manifestation of late-onset homocystinuria. A diagnosis of homocystinuria should be considered in a child or young adult who presents with a stroke. A variety of other symptoms, such as livedo reticularis of the skin, insulin resistance, and diabetes, may also be seen.

MANAGEMENT OF HOMOCYSTINURIA

Homocystinuria can be classified into pyridoxine-responsive and pyridoxine-nonresponsive forms. Genetic studies of general populations show that approximately equal numbers of mutations are responsive and nonresponsive to pyridoxine. However, the majority of patients in whom homocystinuria is detected by newborn screening do not have a response to pyridoxine and have more severe clinical manifestations. If the homocystinuria is left untreated, mental retardation, lens dislocation, osteoporosis, and seizures may develop, and these patients may have thromboembolic events and an early death.[10] Patients who have a response to pyridoxine are unlikely to have had their disease detected on newborn screening.[16] Indeed, the diagnosis of homocystinuria was missed on the newborn screening in this patient. Elevation of homocysteine levels depends on a number of factors, including the level of vitamin B_{12} and the amount of protein in the diet. A newborn who undergoes routine screen-

ing at 2 days of age may have a low protein load and may be replete in pyridoxine and vitamin B_{12} obtained from the mother. Patients with pyridoxine-responsive homocystinuria tend to present later in life with a stroke, skeletal manifestations, or lens dislocation.

Currently, metabolic screening for homocystinuria relies on initial screening for elevated methionine levels in the blood, which, if present, prompt an evaluation of plasma homocysteine and the other metabolites associated with homocystinuria. Homocysteine is not detected well by standard newborn screening, owing to its reactivity to many blood components. The historical cyanide–nitroprusside urine test is no longer in common use and can give false positive results if the patient has been exposed to sulfa drugs or ampicillin, or has a high ketone level.[17]

The goals of treatment for infants with newly diagnosed homocystinuria are normal intelligence and the prevention of thrombotic, ocular, and skeletal complications. In patients whose disease is diagnosed later in life, therapy can prevent the occurrence of potentially life-threatening thromboembolisms and further progression of any complications that have already developed.[15] The first step is to determine whether the patient has pyridoxine-responsive homocystinuria; the determination is made by means of a pyridoxine challenge test in which the patient is given a large trial dose of vitamin B_6 (pyridoxine). In adults, we start with an initial dose of 500 mg; children are administered a lower dose of 100 mg. Pyridoxine administered at a dose of 500 mg over a period of 2 days and then continued for 2 weeks at that dose resulted in a lowering of our patient's homocysteine level to 64 μmol per liter. After 2 weeks, it decreased to 15.8 μmol per liter, which is close to the normal range. High doses of pyridoxine can result in peripheral neuropathy, so this dose is not typically continued beyond a several-week trial period.

Further management strategies include administration of folate and vitamin B_{12}. Low-dose aspirin is administered to decrease the risk of arterial thrombosis. Our patient had taken protein supplements, which probably contributed to his high levels of homocysteine and methionine. We typically restrict the amount of total protein these patients receive in their diet, and we supplement their diet with special formulas that contain protein but that are deficient in methionine. The amount of protein must be monitored; substantial amounts of methionine will boost homocysteine levels, no matter how well these levels are otherwise managed. Betaine (*N*,*N*,*N*-trimethylglycine), which methylates homocysteine, converting it to methionine while bypassing the cystathionine β-synthase enzyme, can be used if needed to further lower homocysteine levels. The elevated level of plasma methionine with betaine is usually harmless. Decreased cystathionine β-synthase levels can result in lower levels of cysteine (Fig. 3) that may need to be supplemented.

Our patient had a low 25-hydroxyvitamin D level (19 ng per milliliter), and he was started on calcium and vitamin D supplementation. Administration of bisphosphonates can be considered in patients with homocystinuria and severe osteoporosis, but they were not used in this case owing to concern that they might impair bone healing after surgical procedures. These patients are at high risk for a vascular event after surgery, and making sure that they are well hydrated before surgery is important. In general, other risk factors for blood clotting, including obesity, smoking, inactivity, prolonged immobilization, dehydration, and the use of oral contraceptives, should be avoided. Women with homocystinuria are particularly at risk for a thrombotic episode in the third trimester of pregnancy.

We have followed this patient closely since his diagnosis. He has been treated with vitamin B_{12}, folic acid, pyridoxine, vitamin D_3, and calcium. The doses of these agents have remained stable, although we decreased his dose of pyridoxine to as low as 50 mg per day. Some patients can be exquisitely sensitive to pyridoxine, requiring only low doses. We were able to transiently decrease his homocysteine level to as low as 9.3 μmol per liter, which is within the normal range. Subsequent levels were mostly between 20 and 29 μmol per liter; a number of fluctuations were attributed to stress and dietary indiscretions. In an attempt to reduce the fluctuations, we have increased his dose of pyridoxine to 200 mg per day, and have worked to keep track of his dietary protein.

Recently, the patient adopted a partial vegan diet, which markedly lowered his homocysteine levels to between 10 and 11 μmol per liter. He has

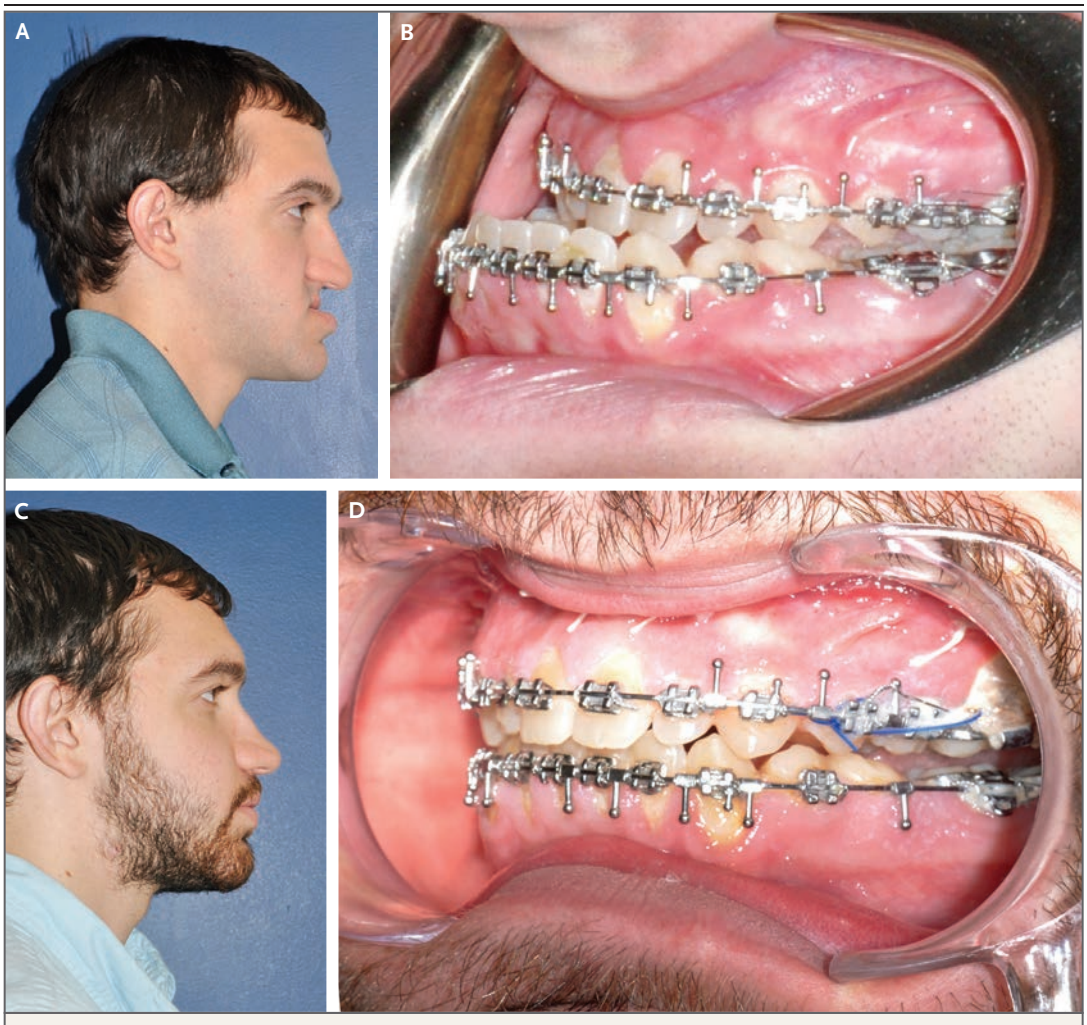

Figure 4. Preoperative and Postoperative Clinical Images of the Face.

A photograph obtained preoperatively shows a lateral view of the midface hypoplasia (Panel A). A second photograph shows a lateral occlusal view, with the braces on the teeth (Panel B). The mandibular teeth extend horizontally beyond the maxillary teeth (negative overjet). A lateral view of the midface shows that after the corrective surgery, the profile is straight (Panel C). A photograph of the occlusion after surgery (Panel D) shows the teeth in normal occlusion (Panel D).

been quite motivated and has been using software to graph his protein and methionine intakes and to view those intakes in relation to his homocysteine levels. It has been satisfying to take care of this young man, who is quite invested in his future and making remarkable progress.

MANAGEMENT OF SKELETAL ABNORMALITIES

Dr. Troulis: This patient's dentofacial deformity (skeletal class III with resultant malocclusion) is a deformity seen in patients with syndromic diseases and in those with developmental deformities (nonsyndromic diseases). The facial features and other conditions raised suspicion of a syndromic cause, and a referral to the medical genetics clinic was recommended, although it turns out that his deformity may not be directly related to the homocystinuria.

To correct the dentofacial deformity, an orthodontist must align the teeth within the arch; orthognathic surgery (LeFort type 1 osteotomy and mandibular osteotomies) must then be performed to advance the maxilla and set back the mandible (Fig. 4). In the case of this patient, to

address considerations specific to the homocystinuria, care was coordinated so that the medical risks from prolonged anesthesia — such as a hypercoagulable state — would be decreased. Providing an adequate diet postoperatively was a concern, since he required a blenderized diet for 6 weeks, although his jaw was not in a state of maxillomandibular fixation.

MANAGEMENT OF OCULAR ABNORMALITIES

Dr. Chen: Subsequently, the patient had several episodes of subacute angle-closure glaucoma in both eyes, as well as at least two episodes of anterior lens dislocation into the anterior chamber. Despite laser iridotomies performed in both eyes, he eventually required more definitive surgical treatment performed by myself and Dr. Demetrios Vavvas of the ophthalmology department at the Massachusetts Eye and Ear Infirmary. We surgically removed both lenses and inserted anterior chamber intraocular lens implants, first in the right eye and then in the left.

Dr. Nancy Lee Harris (Pathology): The patient and his family are with us today and would be happy to answer any questions.

A Physician: When I recall my eating habits in college, I wonder how you have been able to manage your diet in college?

The Patient: This year was kind of a lifestyle change for me. I made the choice to start limiting my consumption of meat, and then I decided to try a completely vegetarian diet. I decided it was manageable, so I continued with it. It's been a few months now. Hopefully, I'll keep with it, but it's tough.

The Patient's Father: When our son decided to try the vegetarian approach, he didn't share his decision with us. I think we knew, as parents, that if we pushed too hard and said, "Try this lifestyle," typically any kid is going to say "Yeah, maybe." When he actually told us he had done it on his own, it was an "Aha!" moment.

Dr. Harris: Is there a way to modify newborn screening to detect the form of homocystinuria that this patient has?

Dr. Sweetser: Methods for improved detection of homocystinuria have been proposed, including parallel testing of total homocysteine levels with the use of acidified samples. Some centers advocate performing a second newborn screening after 2 weeks of life.[16] However, that is logistically challenging and not very practical on a population scale.

A Physician: Has anyone seen this kind of malocclusion in late-onset homocystinuria?

Dr. Troulis: Class III skeletal malocclusion is not uncommon. The maxilla stops growing when patients are between 12 and 14 years of age, but the mandible is the last bone in the body to stop growing. Even though this patient had been screened for Marfan's syndrome, something didn't seem right. But it was really the patient's father, who kept asking me, "Can this all be one diagnosis?" I thought, "Yes."

Dr. Sweetser: The brother's similar (although less extreme) facial features and pectus excavatum suggested the presence of other, undefined familial genetic factors. We're all quite impressed that the patient was referred to us, and I think that is another teaching point of this conference. If there hadn't been a high suspicion for a genetic disorder, he would probably have presented later with more serious complications, such as stroke or even death. There are probably many undiagnosed patients in the general population.

Dr. Harris: This experience illustrates the importance of collaboration between the patient and patient's family, on the one hand, and medical professionals, on the other, because sometimes the patient and patient's family understand things we don't, and so we have to listen. Dr. Richard Cabot, the originator of these conferences, was one of the first American physicians in the early 20th century to emphasize the importance of listening to the patient, and these conferences still teach us, "Listen to the patient."

FINAL DIAGNOSIS

Homocystinuria caused by cystathionine β-synthase deficiency.

This case was presented at Pediatric Grand Rounds.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patient and his family for their willingness to share their information and experiences with our readers; Hong Li, M.D., Ph.D., for her thoroughness and expertise during the initial evaluation of the patient; and Dr. Daniel Doody for his insights into chest-wall defects associated with homocystinuria.

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