Turner Syndrome: A Primer for Internists

Andrew R. Zinn

UT Southwestern Internal Medicine Grand Rounds

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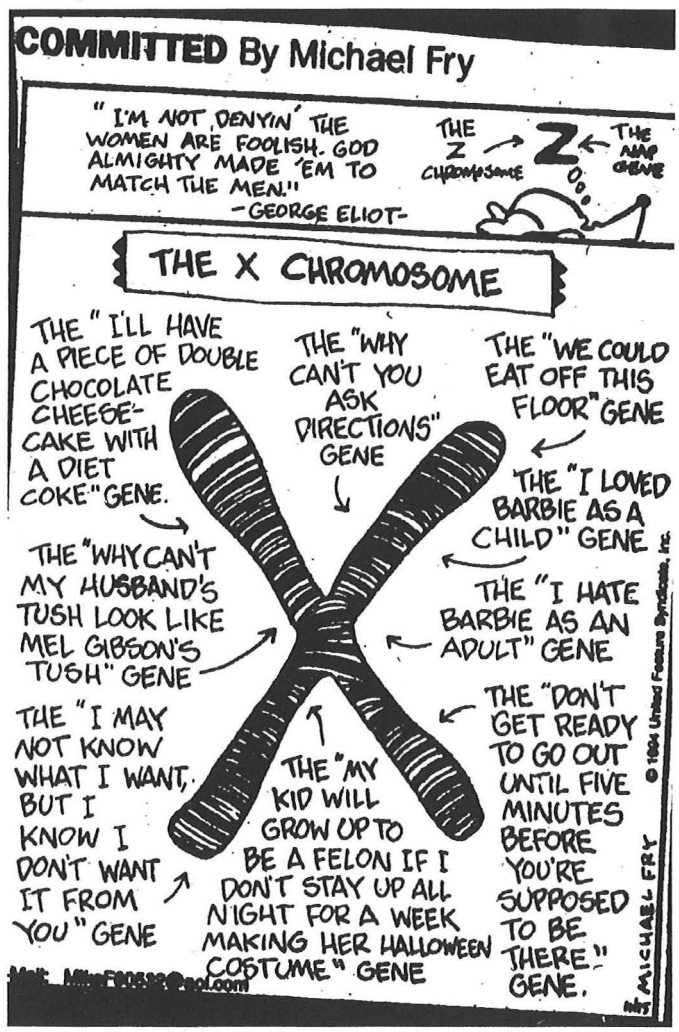

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Andrew R. Zinn, M.D., Ph.D.

Assistant Professor of Internal Medicine

Division of Endocrinology and Eugene McDermott Center for Human Growth and Development

Research interests: genetics of human sex chromosome disorders, infertility, obesity

Email: andrew@mcdermott.swmed.edu

http://www.swmed.edu/home_pages/facultystaff/zinn/index.html

Case Report

AB was a 35 year old Latin-American woman with Turner syndrome and chronic nephrolithiasis of a horseshoe kidney. Past medical history was significant for removal of bilateral streak ovaries in 1992 for treatment of a possible androgen excess syndrome. Her karyotype was 45,X. She was in her usual state of health until January 1995, when she presented to Parkland Memorial Hospital with pyelonephritis and hydronephrosis. She was admitted to the urology service for placement of ureteral stents and treated with parenteral antibiotics, after which she was discharged in stable condition.

She was readmitted on 3/1/95 for staged percutaneous nephrolithotomy. On admission she was afebrile, and physical exam was unremarkable. Urinalysis showed proteinuria, with WBC, RBC, and bacteria present in the sediment.

On the day of admission the patient underwent the first nephrolithotomy procedure under general anesthesia . The procedure was tolerated well. A second procedure was performed two days later to remove the remaining calculi. She again received general anesthesia, this time complicated by transient elevated peak inspiratory ventilatory pressures secondary to right bronchial mainstem intubation. There was no evidence of intraoperative hypoxemia or hypotension.

In the recovery room the patient became acutely hypotensive and tachycardic during extubation and was reintubated. ECG changes included inferior ST segment elevation and anterolatelal ST depression. Acute pulmonary embolism was suspected but was ruled out by pulmonary arteriography, complicated by the abrupt onset of pulmonary edema that was treated with furosemide. Cardiac enzymes peaked the next day, ruling in an acute myocardial infarction, and she was transferred to the CCU.

In the CCU, the patient spiked recurrent fevers to 38.5°C and had an elevated WBC count despite treatment with broad spectrum antibiotics. Multiple blood cultures were negative, and an abdominal CT was negative for renal abscess. Chest x-rays showed progressive bilateral infiltrates, and she remained intubated but hemodynamically stable.

On hospital day 10 her oxygen saturation began to decline, despite an FIO_2 of 60 percent. The next day she received two units of packed RBC's for a hematocrit of 24 percent. Two days later, a urine culture was positive for Candida albicans. Amphotericin B was added but she continued to be febrile, and her pulmonary function continued to decline. On hospital day 15 the patient arrested with electromechanical dissocation. A chest x-ray from earlier that day revealed a left pneumothorax. Emergent chest tube placement and vigorous resuscitation efforts were unsuccessful, and the patient expired.

Postmortem examination revealed severe three vessel coronary artery disease complicated by a recent left posterolateral transmural myocardial infarction. The lungs showed diffuse alveolar damage, consistent with the clinical picture of ARDS. No definitive source of infection was determined; however, fungal forms were present in perinephric sites. The gastrointestinal system showed changes consistent with alcoholic liver disease and remote bouts of pancreatitis. The cause

of death was listed as "multiple insults due to a combination of severe coronary arte[illegible]ease and complications of nephrolithiasis."

As a researcher who studies the genetics of Turner syndrome, I was asked to review this case by anesthesiology and pathology residents and by a staff cardiologist. The specific question was whether premature atherosclerosis is typical of Turner syndrome, and whether this patient should have had a preoperative cardiac workup. I decided to use this occasion to review Turner syndrome, a disorder that affects about 1 in every 3000 live-born girls, emphasizing in particular complications that might be encountered by the internist.

Historical Aspects

Women with Turner syndrome have undoubtedly existed since antiquity. A probable case was described by Morgagni (1682-1771) in his opus, *De sedibus et causis morborum per anatomen indagatis*. Seresevskij described a patient with typical Turner syndrome features in his 1925 address to The Russian Endocrinological Society. In 1930, the German geneticist Otto Ullrich described an eight year old girl [1] in whom the diagnosis of Turner syndrome was later confirmed by karyotype [2]. But the syndrome did not receive much notice until 1938, when the University of Oklahoma endocrinologist Henry Turner described 7 young women with short stature, sexual infantilism, webbed neck, and cubitus valgus (increased carrying angle of the elbow) to The Association for the Study of Internal Secretions [3].

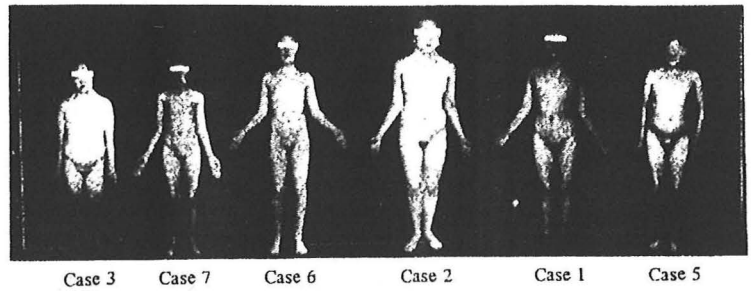

Fig. 1. Turner's original series [3].

Cytogenetics

The chromosomal basis of Turner syndrome was first suspected in the early 1950's from observations that a subset of women with gonadal dysgenesis have no Barr body, or sex chromatin. Polani et al. [4] found that the prevalence of red-green color blindness in females with Turner syndrome (4/25) was similar to that in males (8%), an order of magnitude greater than the prevalence in normal females (0.6%). Since red-green color blindness is an X-linked recessive trait, they reasoned that Turner syndrome females likely have only one X chromosome. With improved cytogenetic methods, Ford, Polani, and colleagues were able to show definitively a few years later that a women with Turner syndrome had an XO (now denoted 45,X) rather than an XY chromosomal constitution (Fig. 2) [5].

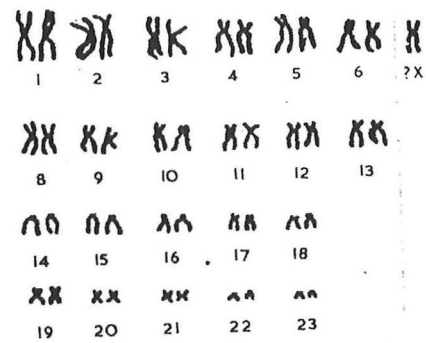

Fig. 2. The first published karyotype of a woman with Turner syndrome showing the absence of one X chromosome [5].

By the mid-1960's it became apparent that a range of karyotypes are associated with Turner syndrome. All involve complete or partial absence of one sex chromosome, or monosomy X (monosomy Y is not viable). Many or probably most Turner syndrome females are mosaic, having two or more cell lines with distinct karyotypes. Mosaicism presumably arises from mitotic errors during embryogenesis. The presence of a normal 46,XX cell line is associated with milder clinical abnormalities, especially when the abnormal karyotype is detected by routine prenatal screening for advanced maternal age or for decreased serum AFP [6]. Mosaicism for an XY cell line also occurs and in some cases leads to the presence of both ovarian and testicular tissue (mixed gonadal dysgenesis). Rare Turner syndrome patients have a nonmosaic 46,XY karyotype, with a portion of the Y chromosome missing. These individuals are female because the portion missing includes the sex-determining gene *SRY* (reviewed by Dr. Keith Parker in these Grand Rounds on 3/12/98).

Karyotypes that include a Y chromosome with or without mosaicism are associated with an increased risk of gonadoblastoma and are an indication for prophylactic gonadectomy. The gonadoblastoma gene(s) (*GBY*) appear to be near the Y centromere [7, 8], and the presence or absence of the *SRY* gene is irrelevant to the risk of gonadoblastoma [9]. Recent studies using sensitive PCR techniques have reported a high frequency of low-level Y chromosomal mosaicism in 45,X Turner syndrome, below the sensitivity of cytogenetics [10-13], but the clinical significance of such low-level mosaicism is unclear [14, 15].

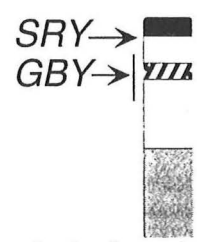

Fig. 3. Relative positions of the male sex-determining gene *SRY* and the gonadoblastoma gene(s) *GBY* on the human Y chromosome.

Today, partial monosomy X is the *sine qua non* for the diagnosis of Turner syndrome. I have even encountered some clinically normal individuals who carry the diagnosis on the basis of a sex chromosome abnormality discovered incidentally, e.g. prenatal

diagnosis. Conversely, patients who fit Turner's clinical description but who have normal karyotypes are never given the diagnosis. Some of these latter patients have Noonan syndrome, an autosomal dominant disorder affecting both sexes (Fig. 4). Identification of specific genes responsible for Noonan and Turner syndrome may reveal the molecular basis for the similar phenotypes.

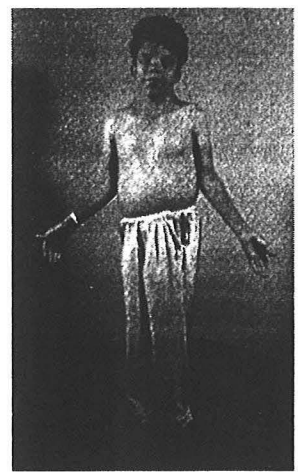

Fig. 4. Patient with Noonan syndrome (courtesy of Dr. Joe Goldstein, UT Southwestern).

The Turner Syndrome Phenotype

The karyotypic diagnosis of Turner syndrome has increased our appreciation of the phenotype associated with the genetic disorder of monosomy X. A principle manifestation is poor viability *in utero* [16]. An estimated 2% of all human conceptuses are 45,X, but fewer than 1% survive to term . Turner syndrome accounts for about 10% of all spontaneous abortions. Lethality most often occurs during early embryogenesis; causes are varied but include severe cardiovascular malformations.

In live-born girls, the features of monosomy X include not only the defects noted by Turner – growth failure, sexual infantilism, webbed neck and increased carrying angle of the elbow (cubitus valgus) – but also a number of other anatomic and physiologic abnormalities. Table 1 lists these features, grouped according to presumed primary embryological defects. Save for growth failure, no feature is invariably present in Turner syndrome, and only a subset of characteristic features are present in any given patient.

Table 1. Turner syndrome abnormalities. From [17].

Primary Defects	Secondary Defects	Incidence (%)
Skeletal growth disturbances	Short stature	100.0
	Short neck	40.0
	Abnormal upper-to-lower segment ratio	90.0
	Cubitus valgus	45.0
	Short metacarpals	35.0

	Madelung deformity	6.6
	Scoliosis	11.5
	Genu valgum	30.0
	Characteristic facies with micrognathia	60.0
	High arched palate	35.0
	Otitis media	75.5
Germ cell abnormalities	1° Gonadal failure	94.0
	Infertility	98.0
	Gonadoblastoma	3.0
Lymphatic obstruction	Webbed neck	23.0
	Low posterior hairline	40.0
	Rotated ears	Common
	Edema of hands/feet	21.0
	Severe nail dysplasia	12.0
Unknown factors – embryologic	Cardiovascular abnormalities	55.0
	Hypertension	6.5
	Renal and renovascular abnormalities	37.0
	Multiple pigmented nevi	25.0
Unknown factors – physiologic, metabolic	Hashimoto's thyroiditis	34.0
	Hypothyroidism	9.0
	Alopecia	1.5
	Vitiligo	1.5
	Gastrointestinal disorders	2.0
	Carbohydrate intolerance	40.0
	Strabismus	16.5
	Ptosis	10.0

Recent studies have also demonstrated characteristic neurocognitive deficits associated with monosomy X [18-22]. These include impaired visual-spatial and visual-perceptual abilities (Fig. 5), recognition of facial affect, dichotic listening and performance IQ. Girls with Turner syndrome typically have a normal Verbal IQ, but the incidence of mental retardation is increased (6%), often associated with a karyotypic variant such as a ring X chromosome [23].

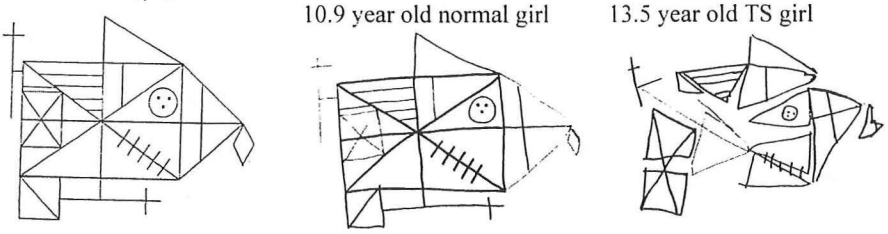

Fig. 5. Rey Osterreith Complex Figure Recall Test [24]. Subjects are asked to reproduce the figure shown in the left panel. (Data courtesy of Dr. Judith L. Ross, Thomas Jefferson University).

Pathogenesis

The pathogenesis of Turner syndrome abnormalities is poorly understood. Dr. Turner suspected that short stature and sexual infantilism were the result of defective secretion of growth hormone and gonadotropins by the anterior pituitary, and he attempted to treat three of his patients with a pituitary hormone preparation and in one case, estrone and estradiol (remarkably, some 60 years later the mainstay of treatment is the same, except that the formulations of growth hormone and estrogen are improved).

It is now thought that growth hormone and IGF-I levels are generally normal in girls with Turner syndrome, and the primary growth defect involves resistance to their action at the post-receptor level [25]. One *in vitro* study showed increased cell doubling time of fibroblasts from patients with partial or complete monosomy X compared to normal cells. Intrauterine growth retardation results in small birth weight. After birth, girls with Turner syndrome fall progressively behind normal girls in height, ending up with a final height on average about 3 standard deviations below the mean, or < 150 cm (4' 11") in the United States.

We now know that the failure to develop secondary sexual characteristics is due to primary ovarian failure and lack of sex steroid production rather than to a pituitary deficiency. Gonadotropin levels in infants and adolescent girls with Turner syndrome are elevated to the range seen in castrate or postmenopausal women [26].

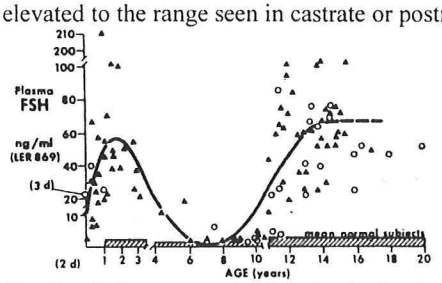

Fig. 6 Plasma FSH levels in different aged patients with Turner syndrome [26]. Triangles, 45,X karyotype. Circles, other karyotypes.

Ovarian failure appears to involve both a reduction in the peak number of primary follicles (normally around 7 million at 20 weeks gestation) as well as accelerated oocyte atresia, the latter probably being the major factor.

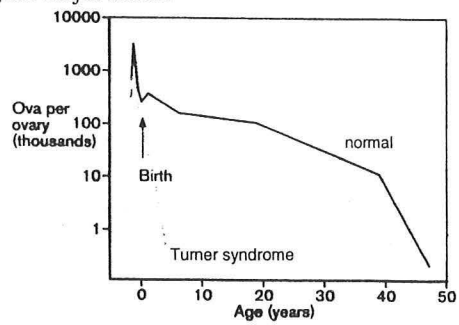

Fig. 7. Germ cell numbers throughout life in normal versus Turner syndrome females. Modified from [27].

Little is known about the etiology of Turner syndrome anatomic abnormalities. 45,X fetuses often exhibit lymphedema, or swelling due to accumulation of interstitial fluid. Anatomic studies of a small number of spontaneous abortuses indicated that the

development of anastomoses between the lymphatic and venous systems in the neck that normally occurs at 6-8 weeks gestation is delayed or absent in fetuses with Turner syndrome. Distension of blind lymphatic vessels and overlying skin is thought to result in webbing of the neck, and in extreme cases, a highly lethal condition known as cystic hygroma (Fig. 8). Congenital lymphedema of the hands and feet is present in about 20% of Turner syndrome girls. Fingernail and toenail abnormalities may be a secondary deformity.

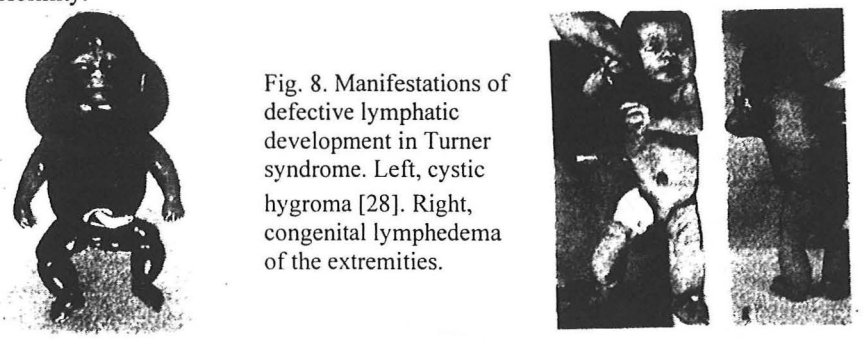

Fig. 8. Manifestations of defective lymphatic development in Turner syndrome. Left, cystic hygroma [28]. Right, congenital lymphedema of the extremities.

Interestingly, there is an association between coarctation of the aorta and webbed neck in TS [29], leading to the hypothesis that coarctation is a deformity secondary to dilated lymphatic vessels impinging on the developing aorta. Alternatively, both abnormalities may due to defective migration of neural crest cells from which both structures are derived embryologically [30]. In support of the latter hypothesis, Miyabara et al. found that 13/13 Turner syndrome fetuses with cystic hygroma had aortic arch and/or valvular abnormalities (Fig. 9) and thymic hypoplasia [31]. In particular, the aortic arch defects they observed ranged from tubular hypoplasia of the ascending aorta to interrupted aortic arch, all corresponding to defects in the left 4th aortic arch derivatives. Similar defects are seen in diGeorge syndrome, which is also thought to involve a defect in branchial arch neural crest cell derivatives [32, 33].

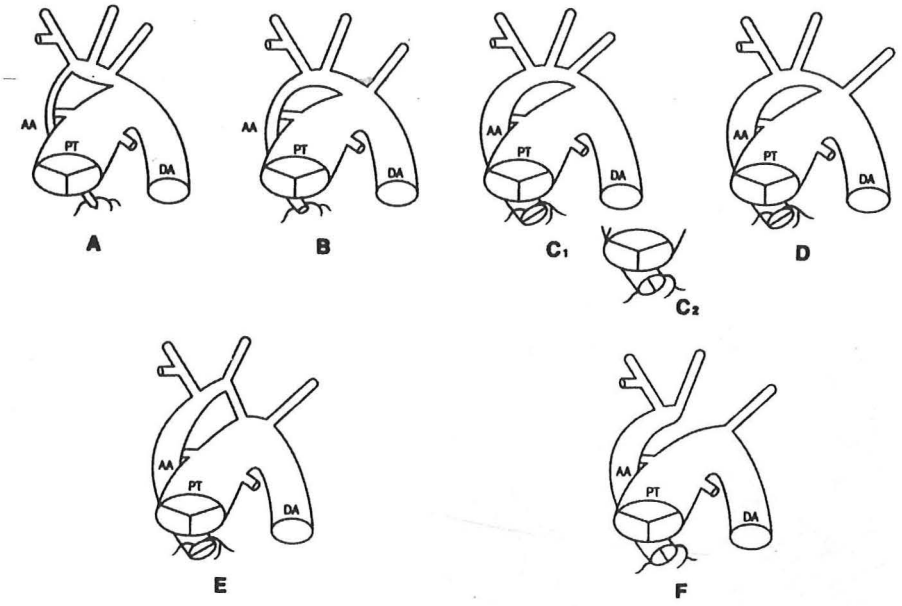

Fig. 9. Schematic diagram of aortic valve and arch abnormalities in 45,X fetuses [31]. A,B: Tubular hypoplasia of the ascending aortic arch and unicuspid (A,B) or bicuspid (C,D,E) aortic valve. F: Interrupted aortic arch and bicuspid aortic valve. AA, ascending aorta; DA, descending aorta, PT, pulmonary trunk.

Molecular Pathogenesis

Several groups have attempted to identify individual genes responsible for specific Turner syndrome abnormalities. The assumption is that two copies of these genes are required for normal development. In other words, Turner syndrome is due to improper gene dosage. You may recall from introductory biology that in female mammals, one X chromosome undergoes inactivation during early embryogenesis (Lyonization), forming the Barr body [34]. Furthermore, normal males have only one X chromosome. How then could some X-linked genes be dosage-sensitive? The answer is two-fold: First, numerous X-linked genes, perhaps as many as 1 in 4, are expressed to varying extents from the "inactive" X chromosome [35]. Second, a number of these genes have counterparts on the Y chromosome that presumably supply the second dose required in males [36].

Recently, a compelling case has been made for the involvement of one of these genes, *SHOX*, in the etiology of Turner syndrome growth failure [37]. The *SHOX* gene is situated at the tips of the X and Y chromosomes, in a small region to which a growth gene has been mapped. It encodes two isoforms of a homeodomain protein that presumably functions as a transcription factor. Both X copies in females and X and Y copies in males are expressed. One isoform is expressed predominantly in bone marrow fibroblasts, consistent with a role in linear growth. Rao et al. [37] found a heterozygous

point mutation in an evolutionarily conserved domain of *SHOX* that cosegregated with isolated short stature in a German family. Interestingly, deletions and point mutations of *SHOX* have also been associated with Leri-Weill dyschondrosteosis [38, 39], a dominantly inherited skeletal dysplasia syndrome characterized by short stature with predominantly mid-limb shortening and, in females, Madelung's deformity (shortening and bowing of the radius with dorsal subluxation of the distal ulna, Fig. 10). Homozygous *SHOX* mutations cause Langer mesomelic dysplasia, a form of dwarfism characterized by severe short stature with hypoplasia/aplasia of the ulna and fibula [39]. Paradoxically, only ~6% of Turner syndrome patients have Madelung's deformity, even though most lack one copy of *SHOX*.

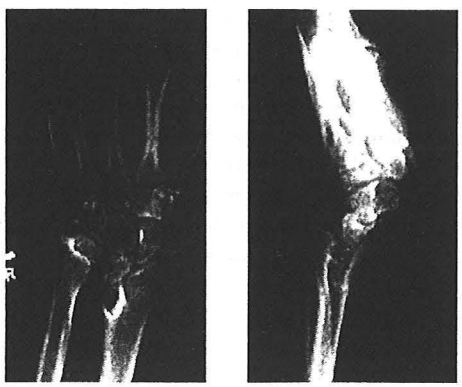

Fig. 10. AP and lateral views of the wrist showing Madelung's deformity.

Complications and Management

Mortality

As was mentioned previously, monosomy X confers a high intrauterine lethality. Increased mortality persists throughout infancy and adult life [40]. A prospective study in the UK of 156 women ascertained through a cytogenetic registry found 15 deaths during an average followup period of 17 years, 4 times the number expected. Five of these deaths were related to congenital heart defects. No other single factor was prominent. The authors estimated that the life expectancy of women with Turner syndrome is reduced by up to 10 years even at age 40.

Cardiovascular

Among the most significant causes of morbidity and mortality are congenital heart defects, most often bicuspid aortic valve (50%) and/or coarctation of the aorta (20%). Evaluation of the heart and great vessels by cardiac ultrasound is part of the routine workup for infants and children with a karyotypic diagnosis of Turner syndrome. MRI may be more sensitive for detecting aortic abnormalities [41], especially in adults (Dr. Beth Brickner, UT Southwestern Medical School). The presence of a murmur is not a sensitive indicator of bicuspid aortic valve [42]. Coarctation should be surgically corrected, and antibiotic prophylaxis for subacute bacterial endocarditis is recommended

for patients with bicuspid aortic valve [43, 44]. There is an increased risk for aortic root dilatation and dissecting aneurysm in women with Turner syndrome, but in 37 of 42 reported cases, a predisposing risk factor (bicuspid aortic valve, coarctation, or hypertension) was present [42]. Recommendations for echocardiographic monitoring of Turner syndrome women without structural cardiac abnormalities varies from never [45, 46] to annually or biannually [47] to every 3 to 5 years [48] and are not based on any prospective studies.

Hypertension is more prevalent in women with Turner syndrome than in the general population, even in the absence of structural cardiac malformations [42]. Other cardiovascular risk factors associated with Turner syndrome include insulin resistance, increased incidence of type II diabetes, and hyperlipidemia [49]. There is also an increased risk of obesity. Overt or subclinical hypothyroidism may contribute to these metabolic abnormalities. The degree to which dyslipemia and insulin resistance seen in Turner syndrome are atherogenic is not known. In adolescents with Turner syndrome not treated with estrogen the lipid abnormalities reflect in part an increase in HDL cholesterol [50]. One cross-sectional study found the relative risk of heart disease and atherosclerosis in Turner patients was 2.11 (95% confidence interval 1.21-3.43) and the relative risk of cerebrovascular disease was 2.71 (95% CI 1.04-5.33) [51]. However, apart from the patient I described at the beginning of these Grand Rounds, I am aware of only one clearly documented case of severe coronary artery disease in a young woman with Turner syndrome [52]. This woman, a 45,X/46,XX Turner syndrome mosaic, suffered an acute MI at age 36. She had no known cardiovascular risk factors and had been treated with oral contraceptives since age 16 for hormone replacement therapy.

On the basis of these scant data, my answer to the question posed at the beginning of this Grand Rounds is that patient AB should have had a preoperative cardiac evaluation, but with the emphasis on identifying structural heart defects rather than coronary artery disease. This evaluation ideally would have been performed at the time she was diagnosed with Turner syndrome. The chart contains no information about other risk factors for ischemic heart disease --- family history, smoking history, lipoprotein profile, blood pressure. Presence of known cardiac risk factors might have increased the index of suspicion of coronary artery disease.

Renal

Renal abnormalities featured prominently in the hospital course of patient AB and indeed were the proximate cause of death. Typical abnormalities seen in Turner syndrome include horseshoe kidney as in AB, absence of one kidney, duplicated ureter, and renal vascular anomalies [53]. Obstruction of the ureteropelvic junction may be asymptomatic, and routine ultrasound evaluation is recommended at the time the diagnosis of Turner syndrome is made. Urinary tract infections are common in girls with Turner syndrome and should be promptly treated to prevent pyelonephritis, as was present in AB. It is not known whether Turner syndrome patients are at increased risk of nephrolithiasis.

Endocrine

Growth failure is one of the principle manifestations of Turner syndrome. Treatment with recombinant human growth hormone therapy has become standard therapy in the United States and many other advanced countries, even though its efficacy remains controversial. Growth hormone therapy in Turner syndrome is the domain of pediatric endocrinologists, and detailed discussion is beyond the scope of today's Internal Medicine Grand Rounds. Suffice it to say that by early next century, most young adults with Turner syndrome will probably have received at least some duration of growth hormone treatment. Whether there are any adverse long term health consequences remains to be seen.

Sexual infantilism is another principle feature of Turner syndrome. Treatment consists of estrogen therapy to induce feminization in a manner that mimics normal sexual maturation as closely as possible, generally initiated between ages 12-15 and complete in 2-3 years. Estrogen is responsible for epiphyseal closure [54]; skillful timing of estrogen replacement vis-à-vis growth hormone treatment is required in order to maximize final height.

Once vaginal bleeding occurs or after 12-24 months of estrogen treatment a progestational agent (e.g. medroxyprogesterone) should be added to induce cyclic menses and prevent endometrial hyperplasia. Hormonal replacement should be continued until at least the normal age of menopause (age 50 or so) to estrogenize the vaginal epithelium, maintain bone density, reduce cardiovascular risk, and reinforce feminine self-image. A typical regimen is 1.25 mg/d of conjugated equine estrogen (Premarin®), with cyclic addition of medroxyprogesterone acetate, 5-10 mg/d for 10-14 days. Note that this dose of estrogen is somewhat higher than that used to prevent osteoporosis in postmenopausal women (typically 0.625 mg/d).

Autoimmune thyroid disease is common in Turner syndrome, leading to hypothyroidism in 10-30% or even more in older patients [55]. Hypothyroidism may exacerbate hyperlipidemia in Turner syndrome [56]. Present recommendations call for measuring TSH at the time of diagnosis, at 1-2 year intervals in children and adolescents, and annually in adults [43].

Insulin resistance is associated with Turner syndrome and is worsened by growth hormone treatment and sex hormone replacement [51]. The incidence of diabetes (both types I and II) is usually said to be no higher than in the general population [44], but one cross-sectional study of hospital diagnoses among Danish women with Turner syndrome found the relative risk of these disorders to be increased approximately 10-fold [51]. Detection bias and/or unique properties of the study population may have contributed to this apparent discrepancy. It would be interesting to know whether the risk of diabetes in Turner syndrome has increased since the criteria for the diagnosis of diabetes were changed [57]

Skeletal

Turner syndrome infants have an increased risk of congenital hip dislocation, which may predispose to degenerative joint disease of the hips in older patients. There is also about a 10% incidence of scoliosis [17].

Osteopenia has long been noted radiographically in women with Turner syndrome [58], and osteoporosis is generally regarded as a feature of the disorder [59]. However, few studies have shown an increased risk of typical osteoporotic fractures (spine, ulna, radius, femoral neck) [49]. Bone mineral density is decreased in women with Turner syndrome [59, 60]. This decrease appears to be due mainly to impaired bone formation during childhood and early adulthood, especially at cortical sites, with deficits at trabecular sites developing later in adulthood [61]. As with most Turner syndrome features, the pathogenesis is multifactorial and may involve abnormalities of calcium-regulating hormones, growth hormone, thyroid hormone, and sex steroids[61]. Two cross-sectional studies indicate the long-term growth hormone therapy during childhood may prevent osteopenia [62, 63]. Similar studies show that long-term estrogen replacement in adults enhances both cortical and trabecular bone density [59, 64-67].

Miscellaneous

Significant conductive and/or sensorineural hearing loss is very common in adults with Turner syndrome [68-70]. Conductive hearing loss may be secondary to recurrent otitis media and poor eustachian tube function, to which girls with Turner syndrome are predisposed as a consequence of craniofacial abnormalities. The etiology of sensorineural hearing loss is unknown; the initial deficit is most severe in the 1.5-2 kHz range, with the addition of progressive high-frequency hearing loss in older women [69].

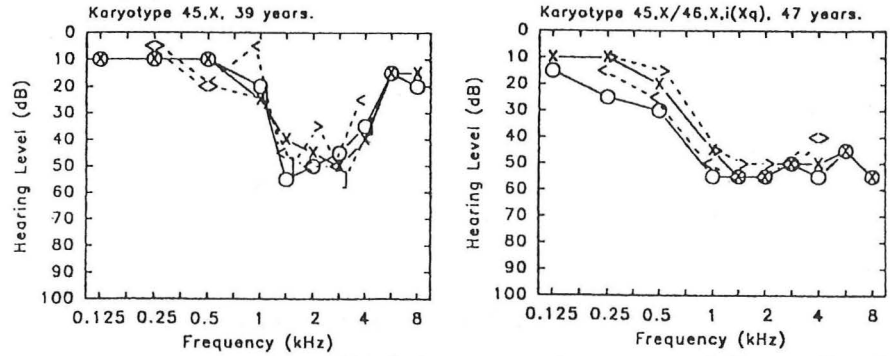

Fig. 12. Audiograms showing typical dip in Turner syndrome women (left), complicated by high frequency hearing loss in older patient (right) [69].

Apart from the previously mentioned risk of gonadoblastoma in patients with Y chromosomal material, there does not appear to be any significant increase in the risk of cancer associated with Turner syndrome, with the possible exceptions of neuroblastoma in children [71, 72] and colon cancer in adults [49, 73]. The latter finding is consistent with a reported increased risk of ulcerative colitis [49, 74, 75]. The risk of Crohn's disease may also be increased [76]. Sex hormone replacement does not appear to increase the risk of breast cancer, and recommendations for screening are the same for women with Turner syndrome as the general population [43, 44].

There may be an increased incidence of cirrhosis in women with Turner syndrome [49]. Although the hepatic changes observed postmortem in patient AB described at the beginning of these Grand Rounds were interpreted as evidence of alcoholic liver disease, one study of 49 middle age women with Turner syndrome found that 82% had elevation of one or more liver enzymes, mainly glutamyl transferase, that did not appear to be related to alcohol consumption [77].

Infertility

Although short stature has received much attention from the medical community, infertility is in fact of greatest concern to most patients [67, 78]. Pregnancies are now possible in women with Turner syndrome or other causes of ovarian failure with in vitro fertilization and donor oocytes, with some centers reporting 50-60% pregnancy rates [44]. These pregnancies should be followed by a team of endocrinologists and perinatologists at a tertiary care facility [79]. Rare women with Turner syndrome have sufficiently preserved ovarian function for spontaneous menstruation and pregnancy. These pregnancies are at high risk of spontaneous abortion, chromosome abnormalities (involving either autosomes or sex chromosomes), and congenital anomalies [80].

Psychosocial and Educational Issues

There is a high prevalence of attention deficit-hyperactivity disorder in young girls with Turner syndrome. School-age girls tend to have problems with peer relations, need for more structure in socialization, and greater difficulty understanding social cues [81-83]. Adult women with Turner syndrome have an increased frequency of psychiatric problems and low self-esteem [84]. There may be an increased risk of anorexia nervosa in adolescents related to this problem of self-esteem compounded by the typical body habitus [85]. Women with Turner syndrome are less likely to marry, tend to do so at a later age, and tend to be older when they leave their parents' home and when they become sexually active than women in the general population [86]. Most adults with Turner syndrome are gainfully employed and live independently [77, 87], although there may be a tendency to seek jobs for which they are overeducated [87]. Most women with Turner syndrome consider their health to be good [88].

The typical nonverbal cognitive deficits associated with Turner syndrome manifest during childhood and persist throughout life. These deficits may cause learning problems, especially with mathematics. Poor visual-motor skills result in clumsiness and poor performance in sports and may be a factor in the increased incidence of radial fractures reported in girls with Turner syndrome [89]. Visual-spatial deficits frequently cause difficulty with driving and map reading. Many girls with Turner syndrome will benefit from early psychosocial and neurocognitive assessment to guide the formulation of a treatment plan tailored to the individual patient. In general, the plan should include extra help with socialization, career and vocational planning, making the transition to independent living, and sex education and orientation to adult sexuality [43].

A 1997 paper in Nature reported the provocative finding from a study of 80 Turner syndrome subjects that social cognitive skills in women with 45,X Turner syndrome are much better if the single X chromosome is derived from the father [90]. This was interpreted as evidence of an imprinted cognitive gene on the X chromosome. The paper received spectacular attention in the lay press (New York Times, Dallas Morning News, etc.) because the authors claimed that this same locus could explain why boys (whose single X chromosome is necessarily inherited from the mother) are more susceptible than girls to behavioral disorders such as autism and attention deficit-hyperactivity disorder.

Like all reports of genes affecting complex behavior (such as controversial "gay" gene [91, 92]), this paper should be viewed skeptically. As yet there has been no independent study to corroborate the finding. Our own study of about 50 girls with 45,X Turner syndrome to date has failed to show any statistically significant differences in neurocognitive measures according to the parental origin of the X chromosome (Judith Ross, personal communication). Furthermore, it is "quite an intellectual leap" to generalize from purported differences among women with Turner syndrome to differences between all males and females (Dr. David Page, quoted in NY Times), given the importance of hormonal and cultural influences on behavior.

Summary

Recommendations for Management of Adults with Turner Syndrome

Karyotype if not done previously.
- Prophylactic gonadectomy if Y chromosome present.

Echocardiography ± cardiac MRI if not done previously.
- Referral to cardiologist for management of structural abnormalities.
- SBE prophylaxis.
- Counsel regarding signs and symptoms of aortic dissection.

Renal ultrasound if not done previously.
- Annual urine cx and BUN/Cr in pts. with anomalies likely to cause obstruction.

Annual blood pressure measurement.

Annual TSH, lipid profile.

Hearing test q. 1-2 years.

Estrogen + progestin up to or beyond usual age of menopause.
- Estrogen: 0.625-1.25 mg Premarine, 1-2 mg micronized estradiol, 0.625-1.25 mg estropipate (Ortho-Est) qd, or Estraderm or Climara transdermal patch (50-100 μg) twice a week.
- Progestin: Cyclic - 5-10 mg medroxyprogesterone acetate or 1-2 mg norethindrome (Aygestin) for 12 days each month. Cyclic combination estrogen and progestin packs are available, e.g Prempro.
  For women who do not wish to menstruate, 2.5-5 mg medroxyprogesterone acetate qd.

Adequate calcium intake, weight-bearing exercise.

Counsel regarding risk of pregnancy if spontaneously menstruating.

Refer for assisted reproduction if pregnancy desired.

Refer to support group.
- Turner Syndrome Society of the U.S.
  http://www.turner-syndrome-us.org/
- Premature Ovarian Failure Support Group
  http://POFSupport.org

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