ОПИСАНИЕ НА ПРЕДЛОЖЕНИЕТО ЗА ЗАБОЛЯВАНЕ в съответствие с чл. 11, ал. 2 от Наредба № 16 от 30.07.2014 г. за условията и реда за регистриране на редките заболявания и за експертните центрове и референтните мрежи за редки заболявания. Издадена от Министъра на здравеопазването, обн., ДВ, бр. 67 от 12.08.2014 г.

ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
Синдром на Turner
Определение на заболяването
Клиничния консенсус дефинира Синдрома на Turner като генетично заболяване, дължащо се на „частична или пълна“ монозомия за Х хромозомата при момичета. Като достоверен източник за идентификация на поне 10 % мозаицизъм с 95 % достоверност се препоръчва стандартно цитогенетично изследване на 30 клетки. Тестуване за генетичен материал с произход от Y хромозома трябва да се проведе при наличие на маркерна хромозома. Най характерния и постоянен клиничен белег е ниския ръст с растежна скорост под 10 персентил за съответната възраст придружен от закъснение в пубертетното развитие и комбинация от някои от следните клинични белези: отоци на ръцете и ходилата, птеригиум коли, ВСМ, особено КоАо или хипопластично ляво сърце, ниско тилно окосмяване, ниско разположени ушни миди, кубитус валгус, хиполастични нокти, множесво пигментни невуси, характерен лицев дисморфизъм, къси четвърти метакарпални кости, високо небце и хроничен среден отит. При поставяне на диагнозата се осъществява скрининг по отношение на съпътстващи аномалии на сърдечно-съдова, отделителна, храносмилателна системи, както и придружаващи други заболявания (вкл. автоимунен тиреоидит). Провежда се и цялостна психологична оценка вкл. КоР(IQ). При клинични индикации-изоставане в растежа и костното съзряване, се започва и се проследява ефекта от хормонално лечение с рчРХ, адаптират се дозите, мониторират се съгласно утвърдени стандарти за странични ефекти, при необходимост се провежда лечение и с други медикаменти, а при достигане на съответна възраст се индуцира и пубертетно развитие.
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
Q96.0 Q96.1 Q96.2 Q96.3 Q96.4 Q96.8 Q96.9
Код на заболяването по Orpha code
ORPHA881.
Епидемиологични данни за заболяването в Република България
Няма епидемилогични данни за заболяването за българската популация. Съгласно големи епидемиологични проучвания в Европа и САЩ синдрома на Turner е с честота 1: 2000-2500 живородени момичета.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Стефанова Е., Л. Пенева. Рекомбинантен човешки растежен хормон в комбинация с малки дози естрогени стимулират растежа и пубертетното развитие при момичета със синдром на Turner. Педиатрия 2010 (1), 49-53
2. Стефанова Е. Л. Пенева. Психологични проблеми при момичета със синдром на Turner. GP News 2011(4), 25-27
3. Е.Стефанова, Л.Пенева. Лечение на Turner syndrome с rhGH в България, X Национален конгрес по ендокринология, 11-14 април 2013, Пловдив
4. Е.Стефанова. Заместително лечение с полови хормони при момичета с Търнер синдром, Практическа педиатрия, 2013, 9
5. Е.Стефанова. Лечение с Растежен хормон в детска възраст, Практическа педиатрия 2014,11, 4-6

Епидемиологични данни за заболяването в Европейския съюз

Пренатална диагноза:
Пренаталната честота на заболяването е много по-висока от постнаталната. Доказателство за това е честотата от 392 на 100 000 женски фетуса със Синдром на Turner, диагностицирани чрез хорион биопсия през 11 г.с. в сравнение с честота след амниоцентеза (16 г.с.) от 176 на 100 000.

Постнатална диагноза:
При проучване проведено в Дания и анализ на резултатите е изчислена честота на Синдрома на Turner 50 на 100 000 момичета и жени. В Дания броят на жените със Синдром на Turner, родени в периода 1970-1993 година и диагностицирани не по късно от 1996 год. е 38 на 100 000, което показва, теоретично, че около 18 момичета и жени на всеки 100 000 са останали недиагностицирани. Осъвременени данни върху честотата в Дания показва, че с напредване на времето допълнително се диагностицират момичета и жени със синдром на Turner. Така през 2006 год. преоценената диагноза е показала честота от 40 на 100 000 живородени момичета за периода 1970-1993.

Заболеваемост и смъртност:
Заболеваемостта е подчертано повишена при Синдром на Turner. При проучване на всички диагностицирани жени със синдром на Turner (n=594; години в риск=5410 години) и общата популация от женски пол в Дания (n=2,594,036) авторите сравняват честота на заболяванията, за които се подозира, че с повишен риск при тази диагноза. Релативния риск (РР) за съпътстващо ендокринно заболяване при пациентка със Синдром на Turner е 4.9 (95% доверителен интервал (ДИ)=3.6–6.4). В тази група се включват хипотиреоидизъм, автоимунен тиреоидит, тип 1 и тип 2 Захарен диабет. По подобен начин и риска от исхемична болест на сърцето (ИБС), артериосклероза, артериална хипертония и мозъчно-съдово заболяване също е повишен. Риска от други заболявания като чернодробна цироза, остеопороза и фрактури също е повишен, както и риска от вродени сърдечни малформации, аномалии на отделителната система, лицето, ушите и шията. РР за всичко карциноми е бил 1.35 (95% ДИ=0.70–2.35), от които само риска от карцином на колона и ректума е значително повишен (РР=4.94).
Смъртността също е значително повишена. При кохортно проучване във Великобритания (n=400, години при риск=8609, смърни случаи=62). РР за смъртен изход е бил 4.2 (3.2–5.4), повишен за сметка на заболявания на нервната, храносмилателната, сърдечно-съдовата, дихателната и пикочо-половата системи. Смърните случаи в следствие на карциноми са били по-малко в сравнение с очакваното,

потвърждавайки датските проучвания. По-рано Price et al. също са намерили 3 пъти повишена смърност, особено при пациетки с вродени аномалии. Авторите в Дания намират общо повишение на отношението смъртност спрямо общата смъртност за популацията от 2.86. Ако смърността се разгледа по причини, то тя е повишена за коронарна болест на сърцето, вродени аномалии, ендокринни и метаболитни болести.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Kirstine Stochholm, Svend Juul, Knud Juel, Rune Weis Naeraa, and Claus Højbjerg Gravholt. Prevalence, Incidence, Diagnostic Delay, and Mortality in Turner Syndrome, The Journal of Clinical Endocrinology & Metabolism 91(10):3897–3902 doi: 10.1210/jc.2006-0558

Оценка на съответствието на заболяването с дефиницията за рядко заболяване съгласно § 1, т. 42 от допълнителните разпоредби на Закона за здравето

Синдрома на Turner съответства с дефиницията за рядко заболяване съгласно § 1, т. 42 от допълнителните разпоредби на Закона за здравето.

Критерии за диагностициране на заболяването

Диагнозата на Синдром на Turner (TS) изисква наличието характерни клинични белези при фенотипни жени , както и пълната или частична липса на втората Х хромозома, с или без клетъчен мозаицизъм. При индивиди с клетъчна популация 45,X, но без клинични белези не се приема диагноза TS. Фенотипни мъже също се изключват, независимо от кариотипа. Като достоверен източник за идентификация на поне 10 % мозаицизъм с 95 % достоверност се препоръчва стандартно цитогенетично изследване на 30 клетки. Тестуване за генетичен материал с произход от Y хромозома трябва да се проведе при наличие на маркерна хромозома. Най характерния и постоянен клиничен белег е ниския ръст с растежна скорост под 10 персентил за съответната възраст придружен от закъснение в пубертетното развитие и комбинация от някои от следните клинични белези: отоци на ръцете и ходилата, птеригиум коли, ВСМ, особено КоАо или хипопластично ляво сърце, ниско тилно окосмяване, ниско разположени ушни миди, кубитус валгус, хиполастични нокти, множесво пигментни невуси, характерен лицев дисморфизъм, къси четвърти метакарпални кости, високо небце и хроничен среден отит.

При поставяне на диагнозата се осъществява скрининг по отношение на съпътстващи аномалии на сърдечно-съдова, отделителна, храносмилателна системи, както и придружаващи други заболявания (вкл. автоимунен тиреоидит). Провежда се и цялостна психологична оценка вкл. КоР(IQ).

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Carolyn A. Bondy, Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group, The Journal of Clinical Endocrinology & Metabolism 92(1):10–25 doi: 10.1210/jc.2006-1374

Алгоритми за диагностициране на заболяването

Диагнозата на Синдром на Turner (TS) изисква наличието характерни клинични белези при фенотипни жени, както и пълната или частична липса на втората Х хромозома, с или без клетъчен мозаицизъм. Най характерния и постоянен клиничен белег е ниския ръст с растежна скорост под 10 персентил за съответната възраст придружен от закъснение в пубертетното развитие и комбинация от някои от следните клинични белези: отоци на ръцете и ходилата, птеригиум коли, ВСМ, особено КоАо или хипопластично ляво сърце, ниско тилно окосмяване, ниско разположени ушни миди, кубитус валгус, хиполастични нокти, множесво пигментни невуси, характерен лицев дисморфизъм, къси четвърти метакарпални кости, високо небце и хроничен среден отит.

При поставяне на диагнозата се осъществява скрининг по отношение на съпътстващи аномалии на сърдечно-съдова, отделителна, храносмилателна системи, опорно-двигателен апарат, зрение и слух, както и придружаващи други заболявания (вкл. автоимунен тиреоидит, целиакия). Провежда се и цялостна психологична оценка вкл. КоР(IQ) и при необходимост пациентката се насочва за специфична работа. Диференциална диагноза се прави с фамилен нисък ръст или конституционално изоставане в растежа и пубертетното развитие, заболявания, които могат да доведат до изоставане в растежа и пубететното развитие, като изолиран дефицит на растежен хормон или в комбинация с дефицит на други тропни хормони на хипофизата, придобити причини за хипопитуитаризъм, други синдроми свързани предимно с нисък ръст като синдром на Noonan и др.

Като достоверен източник за идентификация на поне 10 % мозаицизъм с 95 % достоверност се препоръчва стандартно цитогенетично изследване на 30 клетки. При необходимост могат да се изследват допълнителни метафази, като и да се осъществи флуоресцентна *in situ* хибридизация (FISH). Тестуване за генетичен материал с произход от Y хромозома трябва да се проведе при наличие на маркерна хромозома. Това се осъществява чрез ДНК анализ или FISH , чрез центромерен, а при нужда от късото и дългото рамо на Y хромозомата маркери. Наличието на белези на вирилизация е основание, чрез образна диагностика да се търси гонаден, надбъбречен или срединно разположен тумор и материал от Y хромозома.
При всяко момиче се извършва набор от лабораторни хематологични, биохимични и хормонални изследвания, оценяващи чернодорбна и бъбречна функция, липиден профил, кр. захарни нива вкл. гликиран хемоглобин и полови хормони след 10 год. възраст.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Carolyn A. Bondy, Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group, The Journal of Clinical Endocrinology & Metabolism 92(1):10–25 doi: 10.1210/jc.2006-1374

Daynna J. Wolff, PhD, Daniel L. Van Dyke, Ph D, and Cynthia M. Powell, MD. Laboratory guideline for Turner syndrome, Genetics IN Medicine • Volume 12, Number 1, January 2010

Алгоритми за лечение на заболяването

Целта на лечението е постигане на нормален, съответен на възраста ръст, колкото е възможно по-рано, прогресия на пубертетното развитие в рамките на нормалната възраст и достигане на нормален краен ръст. В основата на това е провеждането на лечение с човешки рекомбиннатен растежен хормон (чрРХ), който увеличава растежната скорост и крайния ръст. Добри прогностични фактори по отношение на крайния ръст са относително висок ръст при започване на лечението, т.е малко изоставане при диагнозата (навременна диагноза), висок родителски ръст, възможност за продължително лечение и достатъчно висока доза. Липсват данни за оптимална възраст на започване на лечението с чрРХ. Лечениетопродължава до достигане на задоволителен краен ръст или до намаление на растежната скорост под 2 см.година или при наличие на малък потенциал за растеж (приблизителна к.в. 14 години). Терапията с чрРХ се проследява и ръководи от детски ендокринолог и пациентите се мониторират през 3-6 месечни интервали. Липсата на спонтанно пубертетно развитие е една от най-честите клинични характеристики на TS. Преди започване на лечение с естрогени се изследват серумните нива на гонадотропните хормони, за да се потвърди липсата на спонтанене пубертет. Естрогеновите препарти могат да бъдат в различна форма доза и начина на приложенеи, но трябва да имитират нормалното пубертетно равитие. Ниска доза (обичайно 1/10 до 1/8 от дозата за възрастен) естроген съдържащ препарат може да бъде започната още на 12 год. възраст. Постепено дозата се увеличава за период от 2-4 години. Най – рано две години след началото на лечението с естроген може да се добави и прогестин.

Момичетата с TS се проследяват и по отношение на автоимунни заболявания вкл. Автоимунене тиреоидит на Хашимото и при наличие на хипотиреоидизъм се провежда и хормонозаместително лечение с L-thyroxin. Провежда се скриниране за целиакия и при доказване на заболяването се преминава на безглутенова диета.
При наличие на вродени аномалии, налагащи хирургично лечение, пациентите се насочват към съответната хирургична клиника.

Клиниката по ендокринология на СБАЛДБ е първата и най-стара детска ендокринологична клиника в страната. В Клиниката се диагностицират момичета със синдром на Turner от самото и създаване като такава в началото на 80-те години на 20 век. От 1993 год. се прилага чрРХ при деца с Хипопитуитаризъм, а от 1995 год. се лекува и момичета със Синдром на Turner. През целия период от 22 години стриктно се мониторират ефектите и нежеланите лекарствени реакции от лечението. В продължение на 3 години лекарите от клиниката са включени и докладват резултати както и регистрирани нежелани лекарствени реакции в KIGS (Pfizer International Growth Database)
До настоящия момент в Клиника по ендокринология са диагностицирани, лекувани и проследени 120 деца с уточнена диагноза С-м на Търнер
През 2012 год. доц. Елисавета Стефанова д.м., ръководител на клиниката защити дисертационен труд на тема "Лечение на изоставането в растежа при момичета със синдром на Turner с рекомбинантен човешки растежен хормон " . Дисертационния труд обхваща над 80 момичета със синдром на Turner, които са диагностицирани и лекувани от нея в Клиника по ендокринология на СБАЛДБ, а ефекта от приложеното лечение е проследен в продължение на 12 год.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

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Алгоритми за проследяване на заболяването

Съгласно приетите консенсуси лечението и проследяването на момичета със Синдром на Turner се ръководи от детски ендокринолог в сътрудничество с кардиолог, генетик, нефролог, дерматолог, офталмолог, УНГ специалист, ортопед, психолог и логопед.
Периодично през 3-6 месечни интервали се проследява ефекта от провежданото лечение по отношение на антропометрични показатели и пубертетно развитие, състояние на сърдечно –съдовата ситема и опорно -двигателната система. Момичетата с TS подлежат на проследяване по отношение на костното съзряване, лабораторни хематологични, биохимични и хормонални изследвания, оценяващи чернодорбна и бъбречна функция, липиден профил, кр. захарни нива вкл. гликиран хемоглобин и полови хормони след 10 год. възраст.
При клинични индикации се извършват консултации със съответен специалист от изброените по-горе.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Carolyn A. Bondy, Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group, The Journal of Clinical Endocrinology & Metabolism 92(1):10–25 doi: 10.1210/jc.2006-1374

Алгоритми за рехабилитация на заболяването

Децата със Синдром на Търнер в повечето случаи не се нуждаят от провеждане на рехабилитация. При наличие на такава нужда пациентите се насочва за работа с клиничен психолог, логопед, изготвя се становище относно специални образователни нужди и необходимост от специална квалификация и професионално ориентиране. Тези дейности са обект на извънболничната помощ и социалните служби по местоживеене.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Carolyn A. Bondy, Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group, The Journal of Clinical Endocrinology & Metabolism 92(1):10–25 doi: 10.1210/jc.2006-1374

Необходими дейности за профилактика на заболяването (ако такива са приложими)

Своевременната диагноза на заболяването осигурява скриниране за вродени аномалии на сърдечно-съдовата, отделителната, гастроинтестналната и др. системи и ранно и навременно лечение вкл. и хирургично. Предпоставка за добър резулат и достигане на нормален краен ръст е провеждане на лечение с чрРХ, което да започне рано и при сравнително малко изоставане в растежа. Индукция на пубертетното развитие при достигане на съответната възраст е възможно само при навременна диагноза.

Момичетата със Синдром на Turner са с повишен риск от развитие на метаболитни нарушение като дислипидемия, нарушен глюкозен толеранс, ЗД тип 1 и тип 2, други ендокриини заболявания като Автоимунен тиреоидит на Хашимото и сърдечно–съдови заболявания, както и остеопороза. Този риск се повишава значително при закъснение с диагнозата и съответното хормонозаместително лечение.
Познаването на заболяването от медицинските специалисти и възможността за диагностика, лечение и проследяване на тези пациентки в специализирани звена би допринесло за намаление на болестността и смъртността сред пациентите със Синдром на Turner.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Carolyn A. Bondy, Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group, The Journal of Clinical Endocrinology & Metabolism 92(1):10–25 doi: 10.1210/jc.2006-1374

Предложения за организация на медицинското обслужване на пациентите и за финансиране на съответните дейности, съобразени с действащата в страната нормативна уредба

Съществуващата в страната система на организация на здравеопазването с възможност пациентите със синдром на Turner да се хоспитализират по клинични пътеки финансирани от НЗОК и в рамките на престоя да се извършват дейности по диагностика, лечение и проследяване на ефекта от лечението осигурява добър достъп до качествени, адекватни и навременни медицински и здравни грижи за пациентките до 18 годишна възраст. След завършване на лечението с чрРХ и навършване на 18 год. възраст, тези пациентки бил следвало да се проследяват от ендокринолог, АГ специалист и кардиолог, а при нужда и от други специалисти в рамките на съществуващата амбулаторна и болнична здравна системи.
Трансфера от проследяващия екип ръководен от детски ендокринолог към специалисти за възрастни обичайно е труден за пациентите и опита сочи наличие на известен интервал до намиране на съответен специалист, който да поеме порасналата пациентка със Синдром на Turner.

Описание на опита с конкретни пациенти със съответното рядко заболяване (ако има такъв)

Клиниката по ендокринология на СБАЛДБ е първата и най-стара детска ендокринологична клиника в страната. В Клиниката се диагностицират момичета със синдром на Turner от самото и създаване като такава в началото на 80-те години на 20 век. От 1993 год. се прилага чрРХ при деца с Хипопитуитаризъм, а от 1995 год. се лекува и момичета със Синдром на Turner. През целия период от 22 години стриктно се мониторират ефектите и нежеланите лекарствени реакции от лечението. В продължение на 3 години лекарите от клиниката са включени и докладват резултати както и регистрирани нежелани лекарствени реакции в KIGS (Pfizer International Growth Database)
До настоящия момент в Клиника по ендокринология са диагностицирани, лекувани и проследени 120 деца с уточнена диагноза С-м на Търнер
През 2012 год. доц. Елисавета Стефанова д.м., ръководител на клиниката защити дисертационен труд на тема "Лечение на изоставането в растежа при момичета със синдром на Turner с рекомбинантен човешки растежен хормон " . Дисертационния труд обхваща над 80 момичета със синдром на Turner, които са диагностицирани и лекувани от нея в Клиника по ендокринология на СБАЛДБ, а ефекта от приложеното лечение е проследен в продължение на 12 год.

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(10):3897–3902

doi: 10.1210/jc.2006-0558

Prevalence, Incidence, Diagnostic Delay, and Mortality in Turner Syndrome

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Aim: Our aim was to study prevalence, incidence, age at diagnosis, and mortality in Turner syndrome (TS) in Denmark.

Methods: Using the Danish Cytogenetic Register, we identified all cases (n = 781) of TS alive in Denmark during 1970–2001. Sixty-nine deceased women with TS were identified in the Causes of Death Register. We divided the cohort into women having the karyotype 45,X, karyotypes including an isochromosome Xq, and all other karyotypes associated with TS. We describe the number of patients diagnosed in Denmark yearly, incidence rates, and the age at diagnosis. Standardized mortality ratios (SMR) were calculated.

Results: A total of 349 women had a 45,X karyotype, 86 had a karyotype including an isochromosome Xq (isoXq), and 346 had another TS karyotype. Mortality was increased in TS with an SMR of 2.86 (95% confidence interval, 2.18–3.55). SMR was increased for coronary diseases, congenital malformations, endocrine diseases, and other causes. The mortality was increased for all types of karyotypes in comparison with the general population but was highest among females with 45,X and isoXq. There was a steady increase in prevalence, but incidence was unchanged. Age at diagnosis was mainly distributed in three periods: less than 1 yr of age (14.9%), during adolescence (10–17 yr) (33.2%), and during adulthood (38.5%), with a median age at diagnosis of 15.1 yr, decreasing during the study period ($P < 0.01$).

Conclusions: Patients with TS and especially the karyotypes 45,X and isoXq have a higher mortality compared with the background population. TS was diagnosed with a considerable diagnostic delay. Prevalence is increasing, but incidence of TS was stable. (***J Clin Endocrinol Metab* 91: 3897–3902, 2006**)

TURNER SYNDROME (TS) is characterized by the absence of part of or the entire X chromosome in a woman, with typical stigmata like short stature, primary amenorrhea, estrogen insufficiency, and cardiovascular malformations. Various karyotypes and phenotypes exist (1). An increased risk of congenital malformations and aortic dissection is seen (2). Increased morbidity is seen, with increased risk of osteoporosis and fractures, type 2 diabetes, ischemic heart disease, hypertension, and stroke (3). An early British report suggested that mortality was also increased (4); however, this study was rather small. In 2001, Swerdlow *et al.* (5) extended the British data and described how mortality in TS is elevated, with an increased risk of death from diseases of the nervous, cardiovascular, respiratory, digestive, and genitourinary systems.

Congenital conditions like TS are present from intrauterine life and onward but may be diagnosed at any point during a lifetime, as opposed to most medical conditions that arise at some point in life and are subsequently diagnosed. Two key epidemiological terms, incidence and prevalence, may therefore easily become confused. In the following, we denote the proportion of a population of females with TS at birth as prevalence at birth (6), and we distinguish between true and known prevalence. We use the term incidence when describing the annual number of cases diagnosed.

We pooled data from a number of cytogenetic studies performed more than 20 yr ago, and based on these studies, we estimated a true prevalence at birth of 50 TS per 100,000 females (pooled population, 48,744 females; pooled TS, 24 females) (7–11). Previously, we found a prevalence of cases diagnosed postnatally of 32 per 100,000 females (12). A considerable delay in diagnosing girls and adolescents with TS was seen in pediatric populations (13, 14), although the delay seems to be diminishing in recent years (14).

To our knowledge, incidence, prevalence, age at diagnosis, and mortality in TS have not been described in an unselected population in a nationwide study. We therefore undertook an investigation among all women with a TS karyotype to study these parameters, including a detailed assessment of all deceased women with TS to identify causes of death.

Patients and Methods

We identified all patients in Denmark diagnosed postnatally with TS in the Danish Central Cytogenetic Register (DCCR) before December 31, 2001. Since 1968 when DCCR was founded, all diagnosed cases of TS in Denmark have been reported from the seven laboratories performing chromosome karyotyping. Data from cases diagnosed before 1968 were also included in the register. The register includes information on karyotype and date of diagnosis and contains approximately 200,000 cytogenetic examinations; of these, 160,000 are prenatal and 40,000 postnatal examinations; the annual number of examinations is approximately 10,000. About 8% of all pregnant women in Denmark were subjected to prenatal analysis during the study period. Some cases of TS are thus diagnosed intrauterine, but few are born because of a high legal abortion

First Published Online July 18, 2006

Abbreviations: CI, Confidence interval; DCCR, Danish Central Cytogenetic Register; HRT, hormone replacement therapy; ICD, International Classification of Diseases; SMR, standardized mortality ratio; TS, Turner syndrome.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

rate of 70–80%, a percentage that has risen through recent years. Only prenatally diagnosed TS cases subsequently verified postnatally are included here, excluding very few prenatally diagnosed cases, not verified postnatally, from the statistical analyses. It is important to stress that the register contains only information regarding karyotype and no information regarding phenotype. Postnatal karyotype examinations are performed based on clinical signs of TS, which differ widely in relation to the age of a given individual (13). Thus, the karyotype of all women with diagnosed TS in Denmark is registered in the DCCR. Part of this cohort has previously been used in a registry study linking DCCR with the National Registry of Patients to describe morbidity (3).

From the Causes of Death Register we obtained a copy of the death certificate for every deceased woman with TS, and from The National Institute of Public Health we obtained the age- and calendar-specific rates for the cause of death divided into 11 International Classification of Diseases (ICD-10) chapters (see Table 2). In the Causes of Death Register, ICD-8 was used from 1969–1993 and ICD-10 from 1994 onward. We translated ICD-8 diagnoses to ICD-10.

For all calculations of mortality, patients entered the study cohort at the date of diagnosis or January 1, 1970, whichever came last. We chose to start the observation period in 1970 to avoid any confounding resulting from a run-in phase in the new DCCR founded in 1968, and we suspect that the mixture of TS females in the early days before systematic registration and karyotyping took place was skewed toward females with a more severe phenotype, possibly introducing an unwanted and hardly controllable bias. Follow-up time ended at the date of death, emigration, or December 31, 1999, whichever came first. All patients were at the latest diagnosed December 31, 1999, and alive at diagnosis. A total of 741 postnatal cases were identified, fulfilling the criterion to contribute time at risk during 1970–1999.

For the calculations regarding prevalence, we focused on 781 cases of TS diagnosed postnatally and alive any time during 1970–2001. For the calculation of incidence, trend in incidence, and median age at diagnosis, we included only patients diagnosed from 1970 onward [n = 704, excluding cases (n = 77) diagnosed before 1970].

The study received approval from the Danish Data Protection Agency and DCCR.

Statistical analysis

Age at diagnosis was studied [median age with 95% confidence intervals (CI) using the binomial distribution), and the differences in median age at diagnosis by karyotype were analyzed using the Kruskal-Wallis test. Time trends in incidence and in median age at diagnosis were analyzed using Poisson and linear regression, respectively. Total and cause-specific standard mortality ratios (SMR) were calculated using 5-yr age groups and 5-yr calendar time periods. The Poisson distribution was used for calculation of exact 95% CI. Kaplan-Meier survival estimates were constructed from age at entry in and age at exit from the cohort. Poisson regression was used to test for differences in mortality among the three groups of females with TS as well as changes in SMR during the study period. $P < 0.05$ was considered significant. Stata 8.2 for Windows (Stata Corp., College Station, TX) was used for all calculations.

Results

Of the grand total of 781 cases, 349 had a karyotype of 45,X, 86 had a karyotype including an isochromosome Xq, and 346 had other TS karyotypes (Table 1). Because of small numbers, we did not subdivide the group of other karyotypes further into karyotype groups containing Y chromosome material or mosaics, such as 45,X/46,XX, which constituted the largest part of this group (n = 120). Preliminary analyses showed that there was no difference between the group 45,X/46,XX and the rest of the subjects in the group of other karyotypes, and we subsequently pooled these two groups in the group of other karyotypes for all other analyses (results not shown).

TABLE 1. Distribution of karyotypes in the study group

Karyotype	N
45,X	349
45,X/46,X,i(Xq); 46,X,i(Xq) or equivalents	86
45,X/46,XX; 45,X/46,X,del(X); 46,X,del(Xp); 45,X/46,X,t(X:X); 46,XXp-; 45,X/46,X,i(Xp); 45,X/46,X,+mar; 45,X/47,XXX	346
Karyotypes containing Y chromosomal material [45,X/46,XY; 45,X/46,X,del(Y)] and others	

Prevalence and incidence

A steady increase in the known number of live TS was observed during the entire study period (Fig. 1). The absolute number of patients diagnosed yearly did not change (Poisson regression $P = 0.39$) during the study period. During 1970–2001, an average of 22 females per year were diagnosed with TS, and approximately 2.6 million women were at risk yearly. Thus, the average incidence rate of TS was 8.5 per million. The cumulated incidence of TS is illustrated in Fig. 2, showing that about 40 TS per 100,000 females have been diagnosed in the cohorts born during 1970–1980, whereas considerably fewer TS females of those born during 1980–2000 have been diagnosed so far.

Age at diagnosis

The median age at diagnosis for the entire TS group was 15.1 yr (95% CI, 14.5–15.8 yr; range, 0–85.4 yr). The age at diagnosis is shown in Fig. 3, and the median age at diagnosis was 13.3 yr (95% CI, 12.1–14.2 yr) for 45,X females, 14.2 yr (12.4–16.2 yr) for females with isoXq, and 19.1 yr (17.8–21.9 yr) for females with any other karyotype. The age at diagnosis was significantly higher in the group of other karyotypes compared with the other two groups (Kruskal-Wallis rank sum $P = 0.0001$). During the study period, we recorded a significant decrease in the median age at diagnosis ($P < 0.01$) (Fig. 4).

Mortality

The overall mortality was increased compared with the general population with an SMR of 2.86 (95% CI, 2.18–3.55)

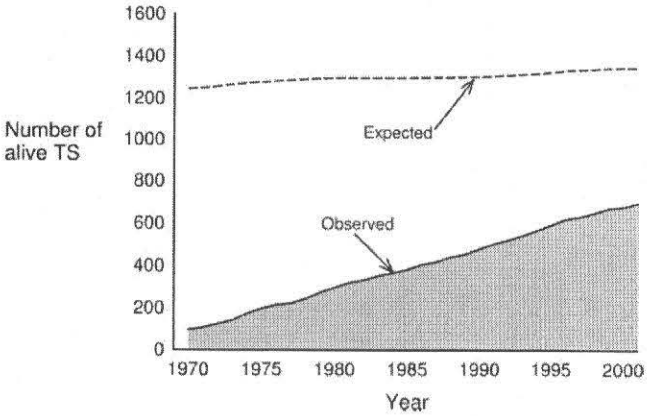

FIG. 1. The absolute number of females with TS during the study period 1970–2001 is illustrated by the *solid line*. Individuals dying or emigrating were subtracted. The *dashed line* indicates the expected number of TS, assuming a true prevalence of 50 TS per 100,000 at birth and similar mortality as in the general population (for details, see *Patients and Methods*).

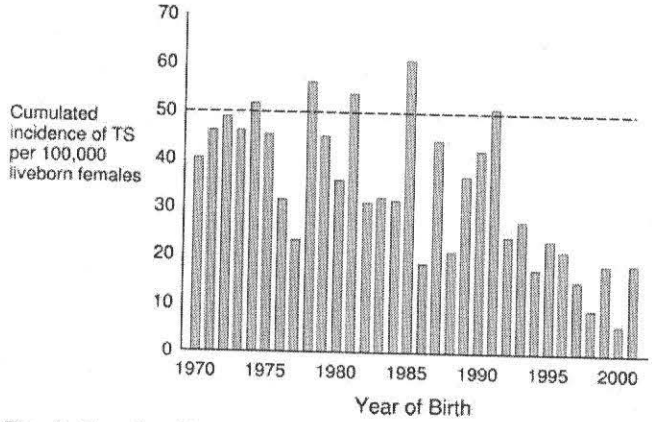

FIG. 2. Cumulated incidence of females with TS born per year during the study period and diagnosed by the end of 2001. The *dashed line* indicates the expected number of TS, assuming a true prevalence of 50 TS per 100,000 at birth and thus corresponding to the expected incidence of TS at birth if all individuals were diagnosed instantaneously. It is obvious from the figure that a number of individuals are awaiting diagnosis.

(Table 2). SMR was significantly increased for all three karyotype groups. Among females with 45,X, SMR was 4.08 (2.79–5.75); among females with isoXq, 3.86 (1.41–8.37); and among other karyotypes, 2.10 (1.42–2.98). Using Poisson regression with the 45,X group as reference group, we found a relative risk of death of 0.94 (95% CI, 0.40–2.26) for females with isoXq, whereas for other karyotypes, the relative risk was significantly decreased at 0.51 (95% CI, 0.31–0.84). Furthermore, we found a tendency toward lower mortality over time although not reaching significance ($P = 0.08$). Mortality in the three groups is illustrated in Fig. 5.

Mortality was significantly increased for endocrine, nutritional, and metabolic diseases, coronary diseases, and congenital anomalies as well as other causes, encompassing a mixed group of accidents, suicide, and unknown reasons (Table 2). Insignificant increases in mortality risk were present for a number of other groups of diseases. We observed a number of different cancers: breast (n = 2), lung (n = 2), colon (n = 2), and urethra, bladder, skin, myeloma, astrocytoma, leukemia, and unknown location (all n = 1). From the individual death certificates, it could be seen that diabetes mellitus was a contributing secondary cause of death in 15 of 69 cases (22%). We observed five cases of dissection of the aorta occurring at the age of 18, 23, 27, 28, and 38 yr.

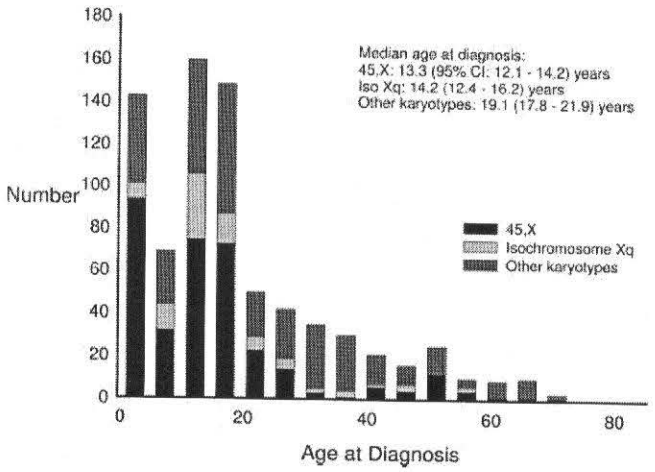

FIG. 3. Age at diagnosis for females with 45,X, an isochromosome Xq, or any other karyotype.

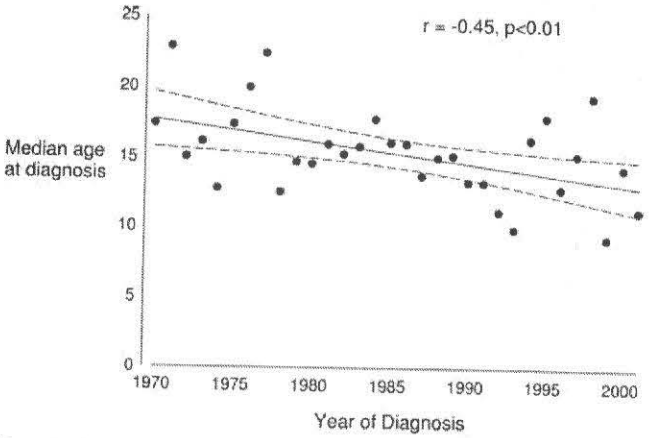

FIG. 4. Age at diagnosis for all TS females during the study period. The *solid line* indicates the regression line, and the *dashed lines* indicate 95% CI. Regression coefficient and significance level are indicated on the graph.

Discussion

Our results show an increased mortality in TS and a considerable delay in diagnosis of the syndrome. The increased mortality is more pronounced than what is seen in another sex chromosome disorder, Klinefelter syndrome (15, 16), but considerably lower than that seen among patients with Down's syndrome (17). The mortality decreased insignificantly during the study period in parallel with a decrease in the population mortality. The recorded prevalence increased during the study period mainly because of the build-up of the register. There was an unchanged incidence during the study period.

We found an overall increased mortality with an SMR of 2.86. Within the group of patients with TS, there were differences, although an increased mortality was present for all chromosomal subgroups. Interestingly, the cause-specific mortality was increased for coronary diseases, congenital malformations, and endocrine, nutritional, and metabolic diseases as well as other causes. However, we could not find an increased risk of dying from pneumonia or other diseases of the respiratory system or of diseases of the digestive and genitourinary systems, as found previously in a smaller group of females with TS (n = 400; deaths, n = 62) in a British study (5). Here, it was also reported that the relative risk of death among TS patients was 4.16 (95% CI, 3.22–5.39). This measure may not be directly comparable with our data, especially because the TS groups studied in Britain and in Denmark differ markedly, the Danish group containing more females with other rarer karyotypes than 45,X known to result in TS, and as a consequence, the fraction of women with the classical karyotype, 45,X, is smaller. We know from previous studies that the fraction of females with TS and karyotypes other than 45,X is increasing in newer studies of TS (12) and that females with karyotypes other than 45,X also suffer from

TABLE 2. Total and cause-specific SMR by main diagnostic groups

	No. of deaths/expected no. of deaths	SMR	95% CI
Infectious and parasitic diseases	1/0.2	4.68	0.12–26.53
Malignant neoplasms	13/7.8	1.67	0.89–2.86
Endocrine, nutritional, and metabolic diseases	3/0.5	5.68	1.17–16.54
Diseases of the nervous system, eye, and ear	2/0.5	4.38	0.53–15.71
Coronary diseases	18/5.2	3.47	2.06–5.48
Cerebrovascular diseases	4/1.8	2.21	0.60–5.66
Congenital anomalies	9/0.4	24.09	11.12–46.18
Diseases of the respiratory system	1/1.5	0.69	0.02–3.82
Diseases of the digestive system	2/1.0	1.96	0.24–7.08
Diseases of the genitourinary system	1/0.3	3.88	0.10–21.43
Other causes	15/5.1	2.95	1.65–4.86
Total	69/24.2	2.86	2.18–3.55
Period[a]			
1970–1979	13/2.8	4.68	2.49–8.00
1980–1989	21/7.34	2.86	1.77–4.37
1990–1999	35/14.05	2.49	1.74–3.46

In addition, total SMR in the different study periods are presented.
[a] Test for trend in mortality during the study period, $P = 0.08$.

increased morbidity (3, 18–21). Discrepancies between our findings and the previous studies could also, in part, be explained by differences in design. We used the same register of causes of death to describe the mortality in both TS and the background population. Data from the Danish Register of Causes of Death are excellent but with a tendency for common causes of death, *e.g.* myocardial infarction, to be overdiagnosed and rare causes, such as cerebral hemorrhage, aortic dissection, and intestinal thrombosis, to be underdiagnosed (22), but we have no reason to believe that the risk of misclassification is different for TS subjects and the background population, and for overall mortality, this is not an issue.

Interestingly, we observed an almost significant decrease in total mortality over the three decades of study. It is not possible to state whether this finding is because of a real decrease in mortality because of better care of individuals with TS or whether it illustrates a change in the composition of the group of TS, with an increased fraction of other karyotypes with time, which we show here to have a lower SMR.

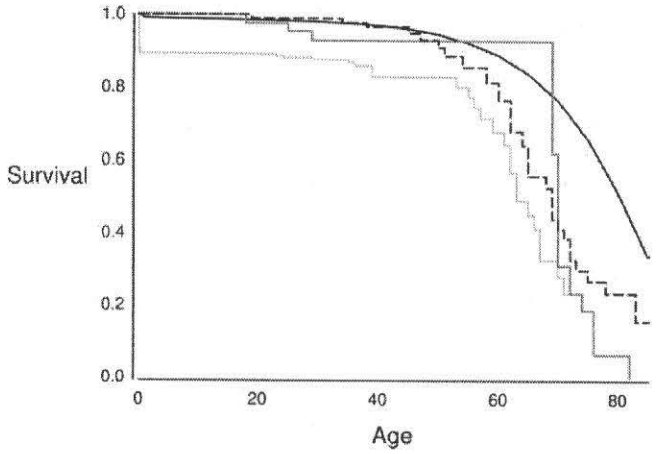

FIG. 5. Kaplan-Meier plots of cumulated mortality in the general population (*black line*), females with 45,X (*light gray line*), females with an isochromosome Xq (*dark gray line*), and females with all other karyotypes associated with TS (*dashed black line*).

The risk of dying from endocrine, nutritional, and metabolic diseases was increased, likely because of an increased frequency of diabetes (3, 20, 23, 24). From studying individual death certificates, it could be seen that diabetes indeed was a frequent contributing cause of death, even in cases where it was not the underlying cause of death. Diabetes may be even more frequent because of possible undiagnosed cases of type 2 diabetes. Thyroid disorders are also frequent in TS (18) but unlikely as underlying causes of death in most cases.

We found a considerably increased risk of congenital anomalies as a cause of death, and although we cannot derive such information from our data, it is likely attributable to malformations of the heart and great arterial vessels. The malformations seen in TS predominantly involve the vessels of the left side of the heart, although venous malformations have also been documented (2, 19, 25–28). Aortic dissection occurs early and with increased frequency in TS (for review, see Ref. 2) and is often accompanied by hypertension, which occurs early in TS (23, 29–31). We recently studied all observed TS cases with aortic dissection in Denmark, including both deceased (included here) and surviving individuals with TS, and estimated that 1.4 in 100 females with TS would suffer from aortic dissection and at a strikingly young age (32). The increased risk of coronary disease may well be explained by the very frequent occurrence of hypertension (~50%) (3, 29, 31, 33); increased carotid intimal thickness, aortic augmentation index, and pulse-wave velocity (34, 35); and lipid abnormalities found by some (36) but not all investigators (23).

Thus, mortality in TS is increased for several reasons, which are potentially amenable to proper treatment. In the present study, we do not know how many were receiving hormone replacement therapy (HRT), but clinically, more than 80% of Danish TS women report the use of HRT (37). Although HRT recently has been nearly abandoned in the postmenopausal setting, there are no data from randomized studies on the impact of HRT on mortality in premenopausal women deprived of endogenous estradiol production. Epidemiological data from female patients in the premeno-

pausal age group with hypopituitarism suggest that treatment with HRT improves survival (38).

The average age at diagnosis of TS of 13, 14, and 19 yr for females with the classical karyotype 45,X, isoXq, or any other karyotype associated with TS is remarkable and surprisingly similar among females with the 45,X and an isochromosome Xq of 13 and 14 yr, whereas individuals with other karyotypes like 45,X/46,XX, deletions of either Xq or Xp, and karyotypes involving a Y chromosome had an even longer median delay of 19 yr. Previously, in a pediatric population, it was shown that the delay to diagnosis was on average 7.7 yr, with a slightly shorter delay of 5.3 yr after an individual had fallen below the fifth percentile for height (13). Likewise, in a Belgian pediatric population, it was found that the median age of diagnosis was 6.6 yr with a wide range of 0–19 yr and improving in comparison with a previous census 12 yr earlier (14). It is not surprising that individuals with karyotypes other than 45,X present longer delays because of the fewer stigmata they typically exhibit; however, studies have also shown unequivocally that women with rarer karyotypes resulting in TS have reduced height and to the same degree as females with 45,X (39–41). Most of these females will also display ovarian failure or very premature ovarian failure (42), and the delay in diagnosis is therefore quite striking; hence the results emphasize the need for increased vigilance of the syndrome among all clinicians. In addition, we estimate that only one tenth of females with TS were diagnosed in 1970, a fraction that had increased to about one half by 2001 (Fig. 1). This information points toward caution when interpreting the present data. But especially interpreting data from older studies, with presumably even more pronounced ascertainment bias, may lead to erroneous conclusions.

The observed increase in prevalence of TS throughout the study period is mainly caused by the build-up of a new registry, with continuing recruitment. Other causes may include a slightly increased diagnostic vigilance among clinicians, leading to a decrease in median age at diagnosis but not to an increase in incidence and perhaps the recorded insignificant decrease in mortality. Changes in the composition of TS karyotypes, with relatively fewer 45,X cases, may also play a role. Our study shows that with a delay of 20–30 yr, most females with clinical symptoms of TS will eventually be diagnosed, anticipating a true prevalence of 50 TS per 100,000 at birth. Of course, our data could also suggest that the true prevalence of TS is even higher and that we do not diagnose all females with TS. The prevalence will of course also be affected by the number of prenatally diagnosed fetuses that are legally aborted. However, because we know that less than 10% of Danish pregnant women have prenatal karyotyping performed, and although a high abortion rate (70–80%) is seen, this figure will only marginally influence the present findings (personal communication with DCCR). This enigma of the true prevalence of TS will be solved only when a complete screening of an entire population is performed. Combining the available data on prevalence, incidence, and diagnostic delay therefore shows that more females with TS are diagnosed today and with a decrease in delay. This decrease in delay to diagnosis may be caused by the contemporary prospects of adequate treatment of reduced height with GH. It is, however, quite clear that new measures need to be taken to diagnose all TS at an early age, and we believe that a karyotype should be included in standard algorithms for the evaluation of short stature.

The limitations of this study are mainly due to lack of clinical data on the subjects. Neither DCCR nor the Causes of Death Register includes any clinical data or data regarding phenotype. The study does not allow determining to what extent the increased mortality among women diagnosed with TS is a direct biological effect of the syndrome *per se* or of hypogonadism and to what extent unfavorable socioeconomic conditions and lifestyle play a role. Furthermore, the cohort of patients is made up of diagnosed cases, and knowing that many females remain undiagnosed, we cannot extend the conclusions of the study to cover such undiagnosed cases.

The strengths of the present study are that this is a nationwide register study, covering all diagnosed TS subjects in Denmark, performed in a uniform public health care system with complete long-term follow-up. By performing standardization for age and calendar time, we were able to adjust for the changing mortality during the decades we were investigating. Furthermore, the study is the largest to date, with the longest study period and 11,030 TS years at risk.

In conclusion, mortality is increased in TS, leading to a considerable decrease in life expectancy. Our data also show a tendency toward a decrease in mortality in TS. Not all individuals with TS are diagnosed, and there is a relatively long diagnostic delay, necessitating more vigilance and knowledge of TS among all clinicians. The prevalence of TS is close to 50 per 100,000 females, but the incidence of TS does not seem to be increasing.

Acknowledgments

Received March 13, 2006. Accepted July 10, 2006.

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The study was supported by Grant 9600822 from the Danish Health Research Council (Århus University Novo Nordisk Center for Research in Growth and Regeneration).

Disclosure of potential conflict of interest: K.S. is supported with an unrestricted research grant from Novo Nordisk. S.J., K.J., and R.W.N. have nothing to declare. C.H.G. previously received lecture fees from Novo Nordisk.

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JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(1):10–25

doi: 10.1210/jc.2006-1374

CLINICAL PRACTICE GUIDELINE

Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group

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Objectives: The objective of this work is to provide updated guidelines for the evaluation and treatment of girls and women with Turner syndrome (TS).

Participants: The Turner Syndrome Consensus Study Group is a multidisciplinary panel of experts with relevant clinical and research experience with TS that met in Bethesda, Maryland, April 2006. The meeting was supported by the National Institute of Child Health and unrestricted educational grants from pharmaceutical companies.

Evidence: The study group used peer-reviewed published information to form its principal recommendations. Expert opinion was used where good evidence was lacking.

Consensus: The study group met for 3 d to discuss key issues. Breakout groups focused on genetic, cardiological, auxological, psychological, gynecological, and general medical concerns and drafted recommendations for presentation to the whole group. Draft reports were available for additional comment on the meeting web site. Synthesis of the section reports and final revisions were reviewed by e-mail and approved by whole-group consensus.

Conclusions: We suggest that parents receiving a prenatal diagnosis of TS be advised of the broad phenotypic spectrum and the good quality of life observed in TS in recent years. We recommend that magnetic resonance angiography be used in addition to echocardiography to evaluate the cardiovascular system and suggest that patients with defined cardiovascular defects be cautioned in regard to pregnancy and certain types of exercise. We recommend that puberty should not be delayed to promote statural growth. We suggest a comprehensive educational evaluation in early childhood to identify potential attention-deficit or nonverbal learning disorders. We suggest that caregivers address the prospect of premature ovarian failure in an open and sensitive manner and emphasize the critical importance of estrogen treatment for feminization and for bone health during the adult years. All individuals with TS require continued monitoring of hearing and thyroid function throughout the lifespan. We suggest that adults with TS be monitored for aortic enlargement, hypertension, diabetes, and dyslipidemia. (***J Clin Endocrinol Metab* 92: 10–25, 2007**)

TURNER SYNDROME (TS) affects approximately one in 2500 live-born females (1). This disorder presents the clinician with a challenging array of genetic, developmental, endocrine, cardiovascular, psychosocial, and reproductive issues. There have been important advances in each of these arenas since publication of the previous recommendations for the care of girls and women with TS (2). This paper is based on the proceedings of a multidisciplinary international conference sponsored by the National Institute of Child Health and Human Development (NICHD) in April 2006. Discussions at this conference and the ensuing recommendations have been based upon recent, peer-reviewed scientific publications. However, there are very few TS studies that would qualify as guidance for evidence-based recommendations, and hence most of the following guidelines represent the experts' consensus judgments given the best information available. The paper is divided into sections addressing 1) diagnostic issues, 2) congenital cardiovascular disease, 3) growth and development, 4) psychological and educational issues, and 5) TS in adulthood.

First Published Online October 25, 2006

* For a list of members of The Turner Syndrome Consensus Study Group, see *Acknowledgments*.

Abbreviations: BAV, Bicuspid aortic valve; BMD, bone mineral density; ECG, electrocardiogram; FISH, fluorescence *in situ* hybridization; MRI, magnetic resonance imaging; OM, otitis media; PAPVC, partial anomalous pulmonary connection; TS, Turner syndrome.

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Diagnostic Issues

Definition

The diagnosis of TS requires the presence of characteristic physical features in phenotypic females (3, 4) coupled with complete or partial absence of the second sex chromosome, with or without cell line mosaicism (5). Individuals with a 45,X cell population but without clinical features are not considered to have TS. Phenotypic males are also excluded from the diagnosis of TS, regardless of karyotype. Whether to diagnose individuals with sex chromosome structural abnormalities as having TS requires clinical judgment. Abnormalities such as ring X and Xq isochromosomes are common in patients with classic TS features, and many of these patients have phenotypes indistinguishable from that of patients with apparently nonmosaic monosomy X (45,X) (5). Patients with small distal short arm deletions (Xp-) including the *SHOX* gene frequently have short stature and other TS-associated skeletal anomalies, but most are at low risk of ovarian failure and should generally not be diagnosed with

TS if band Xp22.3 is not deleted (6). Individuals with deletions of the long arm distal to Xq24 frequently have primary or secondary amenorrhea without short stature or other TS features (7); the diagnosis of premature ovarian failure is more appropriate for them.

Prenatal diagnosis

Sex chromosome abnormalities are increasingly detected prenatally by chorionic villous sampling or amniocentesis, and genetic counseling before any prenatal diagnostic procedure should always include discussion of the possibility of detecting them. Certain ultrasound findings indicate an increased likelihood of TS. Increased nuchal translucency on ultrasound is frequently seen in TS but may also be observed in autosomal trisomy syndromes. The presence of cystic hygromas make the diagnosis of TS more likely (8). Other ultrasound findings suggestive of TS are coarctation of the aorta and/or left-sided cardiac defects, brachycephaly, renal anomalies, polyhydramnios, oligohydramnios, and growth retardation (9). Abnormal triple or quadruple maternal serum screening (α-fetoprotein, human chorionic gonadotropin, inhibin A, and unconjugated estriol) may also suggest the diagnosis of TS (10). Ultrasound and maternal serum screening are not diagnostic, and to make a prenatal diagnosis of TS, karyotype confirmation is obligatory.

The postnatal outcome and constitutional karyotype of individuals with prenatally diagnosed sex chromosome monosomy are uncertain, especially in mosaic cases. Therefore, chromosomes should be reevaluated postnatally in all cases. The degree of mosaicism detected prenatally is not generally predictive of the severity of the TS phenotype (11, 12). In general, any of the features of TS may be seen with virtually any of the common chromosome constitutions (5). Nonmosaic 45,X fetuses with pleural effusion or cystic hygroma often spontaneously abort (13). Nevertheless, a 45,X karyotype, even with ultrasound evidence of cystic hygroma, lymphedema, and effusions, is compatible with delivery of a viable newborn.

Many pregnancies diagnosed prenatally with TS are currently terminated (14, 15). Decisions regarding pregnancy termination are difficult; thus, it is critical that the best available information be provided to parents. Although upholding personal choice about reproduction is a widely embraced ethical principle, decisions to terminate a fetus with TS should never be based upon misunderstood or unbalanced information (16). Many studies providing genotype-phenotype correlations are subject to considerable ascertainment bias. Individuals with 45,X mosaicism detected because of an abnormal antecedent ultrasound study are more likely to have clinical TS than those with 45,X mosaicism detected incidentally by screening on the basis of advanced maternal age (11, 12), which itself is not associated with an increased incidence of TS (17). Outcomes of incidentally detected 45,X/46,XX mosacism are difficult to predict prenatally, but high-resolution ultrasound often provides useful prognostic information. Not unexpectedly, prenatally diagnosed children tend to be less affected than those diagnosed postnatally on clinical grounds (11, 12).

Physicians and genetic counselors involved in pre- and postdiagnostic counseling need to be fully informed about the prognosis, complications, and quality of life of individuals affected with TS as well as of recent advances in management. The clinical spectrum of TS is much broader and often less severe than that described in many textbooks. Prenatal counseling should always involve discussion of the variability of features, the likelihood of short stature and ovarian failure, and their management. It should be emphasized that most individuals with TS have intelligence scores in the normal range, although they may have specific types of learning disabilities. Most adults with TS function well and independently. Girls and women in one study indicated that struggling with their infertility was the greatest challenge they faced in adapting to a life with TS (18). Speaking with children and adults with TS and their families is important for prospective parents faced with a decision about pregnancy and can be facilitated by support organizations, *e.g.* Turner Syndrome Societies.

Postnatal diagnosis

All individuals with suspected TS (see below) should have a karyotype performed. A standard 30-cell karyotype is recommended by the American College of Medical Genetics and identifies at least 10% mosaicism with 95% confidence (19), although additional metaphases may be counted or fluorescence *in situ* hybridization (FISH) studies performed if there is a strong suspicion of undetected mosaicism (20). The cytogeneticist should be consulted in this case. Although a peripheral blood karyotype is usually adequate, if there is a strong clinical suspicion of TS, despite a normal blood karyotype, a second tissue, such as skin, may be examined.

Testing for Y chromosome material should be performed in any TS patient (or fetus) with a marker chromosome (a sex chromosomal fragment of unknown origin, *i.e.* X *vs.* Y). This can be achieved by DNA studies or FISH using a Y centromeric probe, supplemented as necessary by short- and long-arm probes. The presence of virilization in a TS patient should prompt a search for a gonadal, adrenal, or midline tumor as well as investigation of the karyotype for Y material. The prevalence and clinical significance of cryptic Y material detected only by FISH or DNA analysis in patients without virilization or a marker chromosome needs additional investigation. False positives may be a problem with highly sensitive PCR-based Y detection methods (21).

The patient and/or her parents should be informed of the finding of Y chromosome material with the utmost sensitivity regarding gender identity issues to minimize psychological harm. The presence of Y chromosome material is associated with an approximately 12% risk of a gonadoblastoma, according a recent analysis of pooled data (22). Gonadoblastomas may transform into malignant germ cell neoplasms; hence, the current recommendation is for laparoscopic, prophylactic gonadectomy (22). It is often assumed that gonads in patients with TS and Y chromosome mosaicism have no reproductive potential, but spontaneous pregnancies in such women have been reported (23, 24). Thus, preservation of follicles or oocytes may be a future option for some patients undergoing gonadectomy. The gene responsible for gonadoblastoma has not been identified, but mapping data indicate

that it is distinct from SRY, the male sex-determining gene (25, 26). Routine testing for SRY or the presence of Y chromosome material in 45,X individuals without masculinization is not clinically warranted at present.

Indications for karyotype

The diagnosis of TS should be considered in any female with unexplained growth failure or pubertal delay or any constellation of the following clinical findings: edema of the hands or feet, nuchal folds, left-sided cardiac anomalies, especially coarctation of the aorta or hypoplastic left heart, low hairline, low-set ears, small mandible, short stature with growth velocity less than the 10th percentile for age, markedly elevated levels of FSH, cubitus valgus, nail hypoplasia, hyperconvex uplifted nails, multiple pigmented nevi, characteristic facies, short fourth metacarpal, high arched palate, or chronic otitis media (OM).

Newborn screening

Under-diagnosis and delayed diagnosis of TS remains a problem (27). Importantly, early detection permits identification of cardiovascular system malformations such as bicuspid aortic valve that require treatment to prevent complications. Moreover, early diagnosis facilitates prevention or remediation of growth failure, hearing problems, and learning difficulties. Finally, it may be possible in future years to prevent infertility in some individuals with TS by harvesting eggs or ovarian tissue for cryopreservation from girls while they still have viable follicles (28). PCR-based screening methods to detect sex chromosome aneuploidy are feasible (29) but have not yet been validated on a newborn population sample. If and when molecular screening for TS is offered, positive findings will need karyotype confirmation, an infrastructure for follow-up and treatment of the patients with sex chromosome abnormalities, and support services to help parents and caregivers deal with the uncertainties inherent in this type of diagnosis. By extrapolation from experience with prenatal diagnosis, it is highly likely that newborn screening will also identify sex chromosome abnormalities of no clinical consequence in some phenotypically normal individuals; this risk must be weighed against the benefit of early detection of TS and other X-chromosome disorders.

Cardiovascular System

Frequency and type of congenital defects

The most serious, life-threatening consequences of X-chromosome haploinsufficiency involve the cardiovascular system. This is most apparent during fetal development, where major defects in cardiac and aortic development result in a very high mortality for fetuses with a 45,X karyotype (30–32). Fetuses with cardiovascular failure almost always demonstrate obstructed jugular lymphatics with nuchal cystic hygromas. These hygromas resolve as the lymphatics open later in gestation, but residual postnatal webbing of the neck predicts defects such as bicuspid aortic valve (BAV) and aortic coarctation in surviving individuals with TS (33–35). This association led to the hypothesis that the fetal cystic hygromas caused the cardiovascular defects by compressing outflow tracts (33). This view remains speculative, however, and it seems equally possible that haploinsufficiency for the same X-linked gene(s) impairs both lymphatic and vascular development.

Several recent imaging studies have investigated the prevalence of aortic coarctation and BAV in large groups of girls and women with TS (34, 36–38). These studies suggest that on average, approximately 11% have coarctation and approximately 16% have BAV. Aortic coarctation and BAV are each almost 4-fold more frequent in patients with webbed necks, *e.g.* 37% of patients with neck webbing have a BAV compared with 12% in those without webbing (34). It is important to note that coarctation may not be detected in infancy and may be first diagnosed in older children or adults, and magnetic resonance imaging (MRI) studies frequently identify cases missed by echocardiography (39–43). The presence of an abnormal aortic valve is usually clinically silent in young patients and detected only as a result of screening (44). The risks associated with BAV in TS are probably similar to those for nonsyndromic cases. The abnormal valve is at risk for infective endocarditis, and over time, it may deteriorate leading to clinically significant aortic stenosis or regurgitation. The BAV is also associated with aortic wall abnormalities, including ascending aortic dilation, aneurysm formation, and aortic dissection (45, 46).

Recent studies suggest a broader spectrum of cardiovascular system abnormalities in TS than previously recognized. Magnetic resonance angiographic screening studies of asymptomatic individuals with TS have identified a high prevalence of vascular anomalies of uncertain clinical significance (39–42). Almost 50% have an unusual angulation and elongation of the aortic arch termed elongated transverse arch by Ho *et al.* (42). By itself the elongated transverse arch does not appear to be clinically significant, but there is concern that it may reflect an abnormal aortic wall prone to dilation and perhaps dissection. Additional vascular anomalies found in magnetic resonance angiographic studies include partial anomalous pulmonary connection (PAPVC) and persistent left superior vena cava, each affecting approximately 13% (42) *vs.* less than 1% in the general population. PAPVC in TS frequently involves the left upper pulmonary vein, which is less common than the typical right-sided presentation in the general population, and makes echocardiographic detection more challenging. Whether this defect is clinically significant depends upon the degree of the left-to-right shunt (47–49).

There seems to be a generalized dilation of major vessels in women with TS, including the brachial and carotid arteries as well as the aorta. The distal extent of this dilated vasculopathy is unknown. Estrogen deficiency contributes to greater intima medial thickness and altered arterial wall dynamics but not to the increased caliber of vessels (50, 51).

Electrocardiography

Adults with TS have a high prevalence of electrocardiographic conduction and repolarization abnormalities. Right axis deviation, T wave abnormalities, accelerated AV conduction, and QTc prolongation are significantly more com-

mon in women with TS than normal, age-matched controls (52). Right axis deviation may be associated with underlying PAPVC, but the other findings appear independent of anatomic defects (52). These data and the recent observations of an unusual resting tachycardia that begins *in utero* (53) and evidence of impaired sympathovagal tone (54) suggest that there may be an intrinsic defect in autonomic regulation of the cardiovascular system in TS. The clinical significance of these recent observations is unclear, but additional monitoring of electrocardiograms (ECGs) in TS seems warranted.

Risk for aortic dissection

A major concern in TS remains the rare but often fatal occurrence of aortic dilation, dissection, or rupture in relatively young individuals. Dissecting aortic aneurysm in TS is usually associated with additional risk factors including BAV or other abnormalities of the aortic valve, coarctation or dilatation of the aorta, and systemic hypertension (45, 55, 164). Systemic hypertension is common in TS and therefore may be the most important treatable risk factor for aortic enlargement and dissection (46, 164). However, a few cases do not clearly document the established risk factors, raising the possibility that the vasculopathy of TS alone may predispose to dissection. The International Turner Syndrome Dissection Registry has been established in association with the Turner Syndrome Society of the United States to better understand this serious problem (http://www.turner-syndrome-us.org/resource/resources_detail.cfm?id=193).

Screening

All newly diagnosed individuals need a baseline evaluation by a cardiologist familiar with the spectrum of cardiovascular issues encountered in TS (Table 1). This should include two-dimensional and color Doppler echocardiography done in the context of the clinical examination and a baseline ECG. A comprehensive postnatal echocardiogram should be evaluated by a pediatric cardiologist in all infants diagnosed with TS, even in those who had an apparently normal fetal echocardiogram. Echocardiography is usually effective in infants and children but may be limited in some adults because of abnormal thoracic shape or obesity. It is essential that all aortic valve leaflets be clearly visualized to exclude significant abnormalities. If echocardiography is inadequate, computed tomography or cardiac MRI should be performed in a center with expertise in these techniques and should visualize the aortic valve well and provide additional important information about smaller arteries as well as the distal aortic arch and descending aorta. It is important to note that these different modalities may not be directly comparable, and use of a single imaging technique for ongoing monitoring is preferred. All individuals with TS should undergo cardiac magnetic resonance imaging at an age when the study may be performed without sedation. This should be performed at a center with appropriate technical expertise to screen for abnormalities of the aortic arch and descending aorta. If a younger child needs additional imaging on clinical grounds, MRI is an excellent choice even if sedation is necessary.

In addition to screening for anatomic defects, it is important to evaluate the blood pressure and ECG in all newly diagnosed patients. Hypertension affects about 25% of girls and a larger percentage of adults with TS (46, 56, 57). Systemic hypertension is an important risk factor for aortic dilation and dissection. Therefore, blood pressure should be monitored frequently on a regular basis and treated vigorously in all patients with TS. If the baseline ECG reveals a significantly prolonged QTc, then medications that might further prolong the QT should be avoided.

GH treatment and the cardiovascular system

To increase adult stature, most girls with TS are now treated with GH (see *Medical Care for the Child with TS* below). Two echocardiography studies reported normal left ventricular morphology and function in GH-treated girls with TS (58, 59), and two recent MRI studies found no deleterious effect of GH treatment on aortic diameter (60) or compliance (61).

Ongoing care

For the patient that has no identified cardiovascular defects after a comprehensive evaluation, routine pediatric care is advised, with continued monitoring of blood pressure, and a reassessment of the cardiovascular system around the time of transitioning from pediatric to adult care, including MRI, as mentioned above. For normotensive adults with TS who have no underlying cardiovascular disease, the frequency or even the need for continued echocardiographic monitoring is unclear, but it seems prudent to reevaluate aortic dimensions at 5- to 10-yr intervals.

Patients that do have significant cardiovascular defects

TABLE 1. Cardiovascular screening and monitoring algorithm for girls and women with TS

Screening: All patients at time of diagnosis
Evaluation by cardiologist with expertise in congenital heart disease
Comprehensive exam including blood pressure in all extremities
All require clear imaging of heart, aortic valve, aortic arch, and pulmonary veins
• Echocardiography is usually adequate for infants and young girls
• MRI and echo for older girls and adults
ECG
Monitoring: Follow-up depends on clinical situation
For patients with apparently normal cardiovascular system and age-appropriate blood pressure
• Reevaluation with imaging at timely occasions, *e.g.* at transition to adult clinic, before attempting pregnancy, or with appearance of hypertension. Girls that have only had echocardiography should undergo MRI when old enough to cooperate with the procedure
• Otherwise, imaging about every 5–10 yr
For patients with cardiovascular pathology, treatment and monitoring determined by cardiologist

need continued monitoring by a cardiologist, with frequency of monitoring determined by the individual circumstances. Patients with (isolated) hypertension can usually be cared for by a pediatrician or internist, but aortic dimensions need to be determined on a regular basis in these patients. Patients or parents of girls that are considered at increased risk for aortic dilatation or dissection because of the presence of a BAV, coarctation, or hypertension should be educated about this risk, the need for compliance with medical monitoring and treatment, and the possible presenting symptoms, *e.g.* chest or back pain. Patients with multiple risk factors (BAV, dilated aortic root, and hypertension) that put them at high risk for aortic deterioration might want to consider carrying medical information in their wallet or on a bracelet alerting medical personnel to the aortic disease. Such patients also need to be counseled about pregnancy and appropriate exercise programs that do not stress the cardiovascular system. The adult with TS or parents of TS children must be informed that prophylactic antibiotics should be given before tooth or hip surgery.

Monitoring for aortic dilatation

Normal ascending aortic diameter is related to body size and age. Because most individuals with TS are small, one would expect their aortic diameter to be smaller than the average for age-matched control females, but in general it is larger (43, 46). All measurements of the aorta should be done at the end of systole. The ascending aorta should be measured at the level of the annulus at the hingepoints of the valve, at the level of the sinuses of Valsalva perpendicular to the ascending aorta long axis, and at the ascending aorta 10 mm above the sino-tubular junction. Normative data for aortic diameters as a function of body surface area are available (62). Additional measurements that are not as well standardized include measurement of the transverse aortic arch and the descending aorta.

Data on aortic diameters normalized to body surface area for adults with TS are available (46), and a range of absolute diameters from both echo and MRI for women with TS and age-matched controls are also available (43). Review of these data (including echocardiographic ascending aorta diameters measured at the annulus and MRI diameters measured at the level of the bifurcation of the pulmonary arteries) suggests that unadjusted values greater than 28–32 mm will identify patients with diameters greater than 95% of controls, which would clearly be abnormal for women with TS who are generally smaller. When aortic root enlargement is found, medical therapy and serial imaging are recommended. Aggressive control of blood pressure should aim for low-normal values. Because many individuals with TS demonstrate nocturnal hypertension, 24-h monitoring may be helpful in obtaining optimal control (54, 63). In hypertensive patients with aortic root enlargement who also have resting tachycardia, β-adrenergic receptor blockade is an excellent therapeutic option. β-Blockers have been shown to reduce the rate of aortic dilation and dissection in Marfan syndrome (64), although efficacy in treating aortic dilatation in TS has not yet been investigated.

Pregnancy

Spontaneous or assisted pregnancy in TS should be undertaken only after thorough cardiac evaluation. Alarming reports of fatal aortic dissection during pregnancy and the postpartum period have raised concern about the safety of pregnancy in TS (65). If pregnancy is being considered, preconception assessment must include cardiology evaluation with MRI of the aorta. A history of surgically repaired cardiovascular defect, the presence of BAV, or current evidence of aortic dilatation or systemic hypertension should probably be viewed as relative contraindications to pregnancy. For those who become pregnant, close cardiology involvement throughout pregnancy and the postpartum period is essential.

Exercise

In general, heart-healthy exercise (66), in which regular moderate aerobic activity is emphasized, should be encouraged in individuals with TS. Highly competitive sports and very strenuous or isometric exercises are associated with marked increases in heart rate and blood pressure that may have adverse effects on individuals with a dilated aortic root. Therefore, eligibility for competitive sports for all those with TS should be determined by a cardiologist after a comprehensive cardiac evaluation that includes recent MRI of the aorta. Extreme exertion should be discouraged in individuals with significant aortic enlargement. The experts polled on this issue agreed that aortic enlargement in TS may be defined as an aortic sinus of Valsalva or ascending aorta, body size-adjusted Z-score greater than 2 plus evidence of increasing Z-score on a subsequent imaging study of the aorta, or a single Z-score greater than 3. In those cases, participation in competitive sports is contraindicated.

Medical Care for the Child with TS

Once the diagnosis of TS is made, patients should be referred, if at all possible, to a center with expertise in TS and a multidisciplinary approach to treatment. Optimally, members of the pediatric care team should include specialists in pediatric endocrinology, audiology, genetics, cardiology, dermatology, development, nephrology, occupational therapy, ophthalmology, orthopedic surgery, otolaryngology, psychology, and speech therapy. Suggested guidelines for evaluation of newly diagnosed individuals with TS are summarized in Table 2, and a summary of the suggested schedule for ongoing care is given in Table 3.

Lymphatics

Abnormalities of cardiovascular and lymphatic development are found in most TS fetuses that fail to survive the first trimester (31, 32). For those girls that survive, the residua of the fetal lymphedema and cystic hygromas are peripheral lymphedema and webbed neck, the principal keys to diagnosis in the newborn period. The lymphedema seen at birth usually resolves by 2 yr of age without therapy. However, lymphedema may occur or reoccur at any age and may be associated with the initiation of salt-retaining therapies such as GH or estrogen. Some children and adolescents may re-

TABLE 2. Screening at diagnosis of TS in children and adults with TS

All patients
Cardiovascular evaluation by specialist[a]
Renal ultrasound
Hearing evaluation by an audiologist
Evaluation for scoliosis/kyphosis
Evaluation for knowledge of TS; referral to support groups
Evaluation for growth and pubertal development
Ages 0–4 yr
Evaluation for hip dislocation
Eye exam by pediatric ophthalmologist (if age ≥ 1)
Ages 4–10 yr
Thyroid function tests (T_4, TSH) and celiac screen (TTG Ab)
Educational/ psychosocial evaluations
Orthodontic evaluation (if age ≥ 7)
Age > 10
Thyroid function tests (T_4, TSH) and celiac screen (TTG Ab)
Educational and psychosocial evaluations
Orthodontic evaluation
Evaluation of ovarian function/estrogen replacement
LFTs, FBG, lipids, CBC, Cr, BUN
BMD (if age ≥ 18 yr)

BUN, Blood urea nitrogen; CBC, complete blood count; Cr, creatinine; FBG, fasting blood glucose; LFTs, liver function tests.
[a] See Table 1.

quire support stockings and elevation for treatment. Complete decongestive physiotherapy, a four-step process involving skin and nail care, massage for manual lymph drainage, compression bandaging, and a subsequent remedial exercise regimen (67) is recommended for those with more significant lymphedema (68). Long-term diuretic use should be avoided because of its marginal efficacy and problems with fluid and electrolyte imbalance. Vascular surgery should be avoided. Families can be directed toward The National Lymphedema Network (http://www.lymphnet.org) for more information.

Urinary system

Congenital malformations of the urinary system are present in 30–40% of patients with TS (69, 70). By ultrasound, collecting-system malformations are found most frequently (~20%), followed by horseshoe kidneys (~10%) and malrotation and other positional abnormalities (~5%). If an iv pyelogram is also used for screening, even more abnormalities will be identified, but these tend to be clinically insignificant (71). All girls with TS should have a renal ultrasound study performed at diagnosis. Structural malformations of the kidney occur more frequently in 45,X TS, whereas collecting-system malformations occur more frequently in those with mosaic/structural X karyotypes. In a recent study (69), no patient with a normal baseline ultrasound developed renal disease during a follow-up period averaging 6 yr. However, some of those with malformations developed hypertension and urinary tract infections.

TABLE 3. Ongoing monitoring in TS

All ages
Cardiological evaluation as indicated[a]
Blood pressure annually
ENT and audiology every 1–5 yr
Girls <5 yr
Social skills at age 4–5 yr
School age
Liver and thyroid screening annually
Celiac screen every 2–5 yr
Educational and social progress annually
Dental and orthodontic as needed
Older girls and adults
Fasting lipids and blood sugar annually
Liver and thyroid screening annually
Celiac screen as indicated
Age-appropriate evaluation of pubertal development and psychosexual adjustment

[a] See Table 1.

Eye

Abnormalities of the external ocular adnexa including epicanthal folds, ptosis, hypertelorism, and upward slanting palpebral fissures are common in TS (72). Red-green color deficiency is present in approximately 8% of the population, a percentage similar to that found in males. Most importantly, strabismus and hyperopia (farsightedness) each occur in 25–35% of these children, putting them at high risk for amblyopia. To promote early detection and treatment and prevent visual loss, children with TS should be evaluated by a pediatric ophthalmologist at 12–18 months of age in addition to receiving routine ophthalmological evaluations by their primary care physician.

Ear

Hearing problems and ear malformations are common in TS and correlate with karyotype (73, 74). There is a high prevalence of OM that may result from an abnormal relationship between the eustachian tube and middle ear, a consequence of abnormal cranial base anatomy. As the result of OM, conductive hearing loss is common in young girls with TS (75). Although a more significant issue in adulthood, progressive sensorineural hearing loss with a unique dip in the 1.5- to 2-kHz region and/or a high frequency loss (above 8 kHz) may present as early as 6 yr of age and necessitate the use of hearing aids in childhood.

Heightened surveillance for middle ear effusions should occur in girls with TS until at least 7–8 yr of age, and longer for those with a history of OM. Evaluation should include otoscopic examination, preferably pneumatic otoscopy, tympanometry, or both on at least an annual basis. Therapy for OM in girls with TS should be managed aggressively because of the significant impact that hearing loss can have on speech and language development and the risk of cholesteatoma formation in those with persistent otorrhea. TS girls should be evaluated for persistence of middle ear fluid approximately 6–10 wk after an episode of acute OM to document whether the effusion has cleared. Girls that have middle ear effusions persisting longer than 3 months or recurrent episodes of acute (suppurative) OM should be referred to an otolaryngology specialist. Common surgeries for recurrent OM and airway problems include tympanostomy tube placement, tonsillectomy, and adenoidectomy. Removal of the adenoids may exacerbate palatal dysfunction and negatively influence quality of speech, factors that must be taken into consideration before surgery.

Girls or women diagnosed with TS at an older age should

be referred to an audiologist at the time of diagnosis. For those with a history of OM or hearing loss, audiological evaluations are recommended annually or as per their audiologist. In older girls and women with TS with no history of hearing loss, audiological surveillance is warranted every 2–3 yr.The assiduous treatment of ear-nose-throat problems in childhood and avoiding additional potential injuries to the inner ear may reduce the risk of hearing loss.

Orthodontics

Distinct craniofacial features in TS include a flattened cranial base angle, a marked reduction in posterior cranial base length, and a retrognathic face (76). The maxilla is generally narrow with a high, arched palate, whereas the mandible tends to be wide and micrognathic. The prevalence of distal molar occlusion, anterior and lateral open bite, and lateral crossbite are significantly increased (77). Abnormalities in tooth development and morphology include early eruption of the secondary teeth, simple crown morphology, thinner enamel, less dentine, and short roots (78). Girls with TS are also at greater risk for root resorption, which can lead to tooth loss, especially during orthodontic treatment. It is recommended that all girls with TS see a pediatric dental specialist by the age of 2 yr and an orthodontist no later than age 7 yr. Because GH treatment can alter craniofacial proportions, all girls with TS treated with GH should receive periodic orthodontic follow-up (79). Prophylactic antibiotics should be used before dental procedures in TS with known cardiac malformations.

Autoimmunity

Individuals with TS clearly have increased risk for autoimmune thyroiditis and celiac disease. Autoimmune thyroid disease is common during childhood in TS and has been reported as early as 4 yr of age (80, 81). In a recent study, 24% of 84 children with TS (0–19 yr old) who were followed longitudinally (mean duration, 8 yr) developed hypothyroidism and 2.5% developed hyperthyroidism (80). Generally, there are no overt clinical symptoms of hypothyroidism. Although thyroid antibodies identify patients at high risk, all patients with TS should be screened annually for autoimmune thyroid disease with a TSH and T_4 from 4 yr of age onward.

The risk of celiac disease is increased in TS, with 4–6% of individuals affected (82). As recommended by North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines (83), TS girls should be screened by measurement of tissue transglutaminase IgA antibodies. Periodic screening should begin at age 4 and be repeated every 2–5 yr. If HLA typing is performed, individuals without DQ2 or DQ8 need no additional antibody measurements.

Skin

An increased number of acquired melanocytic nevi is seen in TS (84), but the risk for melanoma does not appear to be increased (85). A reputed propensity toward keloid formation may be a reflection more of the sites at which individuals with TS commonly undergo plastic surgery (head, neck, and upper chest) rather than an intrinsic difference in healing (86).

Skeletal system

Short stature is probably the most common, readily recognizable clinical feature of TS. Much of the deficit in height is caused by haploinsufficiency of the short-stature homeobox-containing gene (*SHOX*) located within the Xp-terminal, pseudoautosomal region of the X chromosome (87). It affects virtually all individuals with TS and results in an average adult stature 20 cm shorter than their target height (88, 89). The typical growth pattern in TS is characterized by mild intrauterine growth retardation, slow growth during infancy, delayed onset of the childhood component of growth, growth failure during childhood, and the absence of a pubertal growth spurt.

Skeletal abnormalities encompass more than poor linear growth. Disproportionate growth causes many girls with TS to appear stocky, with a wide body and relatively large hands and feet (90). In addition, developmental abnormalities of individual bones account for many common findings such as short neck, cubitus valgus, genu valgum, and short fourth metacarpals. Madelung deformity of the wrist, although often mentioned in connection with TS, is actually rather infrequent (91). Infants with TS have an increased risk of congenital hip dislocation. Girls with TS have higher risks for scoliosis and kyphosis than the general population; 10–20% of girls with TS develop scoliosis, and kyphosis and/or vertebral wedging also appears to be more common (92, 93). The latter may be quite difficult to appreciate clinically, and both problems can progress with rapid growth. Phalangeal bone density has been reported to be normal during childhood (94).

Growth-promoting therapy

The goals of growth-promoting therapies are to attain a normal height for age as early as possible, progress through puberty at a normal age, and attain a normal adult height. The centerpiece of growth-promoting therapy is GH, which increases growth velocity and final adult stature. Girls with TS generally have a normal GH secretory pattern (95). Provocative GH testing should be performed only in those whose growth is clearly abnormal relative to that expected for TS, determined by plotting lengths and heights on TS-specific growth curves (88, 89, 96, 97).

It is well established that GH therapy is effective in increasing final adult height. However, the magnitude of the benefit has varied greatly depending upon study design and treatment parameters. In the first randomized controlled trial to follow GH-treated TS subjects to final height (98), the Canadian GH Advisory Committee corroborated the increases in adult stature reported by studies with historical controls (99–102). In the Canadian study, girls with TS (aged 7–13 yr) who were randomized to receive GH (0.3 mg/kg·wk; maximum weekly dose, 15 mg) achieved a final adult stature 7.2 cm taller than the control group after an average of 5.7 yr. Factors predictive of taller adult stature include a relatively tall height at initiation of therapy, tall parental heights,

young age at initiation of therapy, a long duration of therapy, and a high GH dose (103–108).

The optimal age for initiation of GH treatment has not been established. Preliminary data from the Toddler Turner Study, in which 88 girls between the ages of 9 months and 4 yr (mean age, 2.0 yr) were randomized to GH or no GH therapy, indicate that GH therapy is effective beginning as early as 9 months of age (109). In addition, the safety profile appears to be similar to that observed in older TS children. Treatment with GH should be considered as soon as growth failure (decreasing height percentiles on the normal curve) is demonstrated and its potential risks and benefits have been discussed with the family.

GH therapy in the United States is generally initiated at the FDA-approved dose of 0.375 mg/kg·wk. This is most effective when given daily and customarily administered in the evening. The dose can be adapted according to the patient's growth response and IGF-I levels. Growth prediction models may be helpful in determining the potential effects of changes in dosing (103). Doses substantially higher than those approved by the FDA (0.054 mg/kg·d = 0.162 IU/kg·d = ~4.8 IU/m^2·d) produce a relatively small gain in final height, although there is no apparent increase in short-term adverse events (110). For example, in a study by the Dutch Working Group, the mean gain in final height in groups treated with 4 IU/m^2·d (0.045 mg/kg·d), 6 IU/m^2·d and 8 IU/m^2·d averaged 11.9 ± 3.6, 15.7 ± 3.5, and 16.9 ± 5.2 cm, respectively (99). However, when GH was given at the higher doses, IGF-I levels were often above the normal range, and ideally, prolonged exposure to elevated IGF-I levels should be avoided because of theoretical concern about potential long-term adverse effects (111).

For girls below approximately 9 yr of age, therapy is usually started with GH alone. In older girls, or those with extreme short stature, consideration can be given to using higher doses of GH and adding a nonaromatizable anabolic steroid, such as oxandrolone (100). The dose of oxandrolone should be 0.05 mg/kg·d or less, and liver enzymes should be monitored. Higher doses are likely to result in virilization (clitoral enlargement, acne, lowering of the voice, *etc.*) and more rapid skeletal maturation. Therapy may be continued until a satisfactory height has been attained or until little growth potential remains (bone age ≥ 14 yr and growth velocity < 2 cm/yr). GH therapy should be directed by a pediatric endocrinologist and the child monitored at intervals of 3–6 months. Evaluation for orthopedic problems as well as growth velocity should be part of the regular physical examination. Development of scoliosis or kyphosis does not necessarily preclude GH therapy; however, close collaboration with an orthopedic surgeon is required.

Puberty induction

Absent pubertal development is one of the most common clinical features of TS, although up to 30% or more of girls with TS will undergo some spontaneous pubertal development (112, 113), and 2–5% may achieve spontaneous pregnancy (114). Ultimately, over 90% of individuals with TS will have gonadal failure. Before initiation of estrogen therapy, serum gonadotropin levels should be determined to exclude the possibility of delayed spontaneous pubertal development.

When estrogen therapy is required to induce pubertal development, the form, dosing, and timing should reflect the process of normal puberty (Table 4). Delaying estrogen therapy until 15 yr of age to optimize height potential, as previously recommended (115), seems unwarranted. This emphasis on stature tends to undervalue the psychosocial importance of age-appropriate pubertal maturation and may be deleterious to bone and other aspects of the child's health (116–118). Furthermore, recent evidence suggests that some treatment regimens using estradiol that begin replacement at the age of 12 yr permit a normal pace of puberty without interfering with the positive effect that GH has on final adult height (99, 116, 119, 120).

Many forms of estrogen are available, and oral estrogens have been most often used. However, both transdermal and injectable depot forms of estradiol may be more physiological alternatives (116, 119–121). Low-dose estradiol therapy can be initiated as early as 12 yr of age. Replacement is

TABLE 4. Ovarian hormone replacement treatment in TS

Age (yr)	Age-specific suggestions	Comments
10–11	Monitor for spontaneous puberty by Tanner staging and FSH level	Low-dose estrogen treatment may not inhibit GH-enhanced growth in stature
12–13	If no spontaneous development and FSH elevated, begin low dose E2	Equivalent initial E2 doses: depot (im) E2, 0.2–0.4 mg/month; transdermal E2, 6.25 μg daily[a]; micronized E2, 0.25 mg daily by mouth
12.5–15	Gradually increase E2 dose over about 2 yr (*e.g.* 14, 25, 37, 50, 75, 100, 200 μg daily via patch) to adult dose	Usual adult daily dose is 100–200 μg transdermal E2, 2–4 mg micronized E2, 20 μg EE2, 1.25–2.5 mg CEE
14–16	Begin cyclic progesterone treatment after 2 yr of estrogen or when breakthrough bleeding occurs	Oral micronized progesterone best option at present; usual adult dose is 200 mg/d on d 20–30 of monthly cycle or d 100–120 of 3-month cycle
14–30	Continue full doses at least until age 30 because normally estrogen levels are highest between age 15 and 30 yr	Some women may prefer using oral or transdermal contraceptive for HRT; monitor endometrial thickness
30–50	The lowest estrogen dose providing full protection *vs.* osteoporosis is 0.625 CEE or equivalent	Monitor osteoporosis risk factors, diet, exercise; obtain BMD and begin regular screening mammography by age 45 yr
>50	Decision on estrogen use based on same considerations as for other postmenopausal women	New HRT options are appearing, and these recommendations may need updating in near future

CEE, Conjugated equine estrogens; E2, estradiol; EE2, ethinyl estradiol; HRT, hormone replacement treatment.

[a] The lowest-dose commercially available E2 transdermal patches deliver 14 and 25 μg daily; it is not established whether various means of dose fractionation (*e.g.* administering a quarter patch overnight or daily or administering whole patches for 7–10 d per month) are equivalent.

usually begun at one tenth to one eighth of the adult replacement dose and then increased gradually over a period of 2–4 yr. The following are equivalent doses that achieve estradiol levels in the normal range for young adult women: oral estradiol, 2 mg/d; transdermal estradiol, 0.1 mg/d; and injectable estradiol cypionate, 2.5 mg/month. To allow for normal breast and uterine development, it seems advisable to delay the addition of progestin at least 2 yr after starting estrogen or until breakthrough bleeding occurs. The use of oral contraceptive pills to achieve pubertal development is best avoided, because the synthetic estrogen doses in most formulations are too high and the typical synthetic progestin may interfere with optimal breast and uterine development. It is important to educate the patient that estrogen replacement is usually required until the time of normal menopause to maintain feminization and prevent osteoporosis (118).

During the process of pubertal development, it is important to engage the patient in a gradual discussion about how TS and its treatment may impact her sexual development and function and reproductive potential. In addition, when appropriate, counseling for the prevention of sexually transmitted diseases (and unwanted pregnancy for those with endogenous ovarian function) should also be provided.

Transition management

The transition from pediatric to adult health care should occur at the completion of growth and puberty during late-stage adolescence (usually by age 18 yr). However, the transition should be initiated as a staged process. Beginning at approximately age 12, the center of care should be shifted incrementally from the parent to the adolescent with TS. The health care focus also shifts from maximizing height to inducing feminization, counseling the adolescent with TS about the evolving impact of her condition into adulthood and promoting the development of independent self-care behaviors.

Transition is an appropriate time to assess individual risks for potential adult morbidities and promote healthy lifestyles. To help ensure adequate bone mineral accrual, girls with TS are encouraged to have calcium intake of more than 1000 mg of elemental calcium daily in the preteen years and 1200–1500 mg daily after 11 yr of age. This will generally require oral supplementation. Counseling as to healthy eating and exercise habits and maintaining a healthy weight are essential. During late-stage transition, the pediatric endocrinologist should engage the transition patient in developing an adult care plan in close collaboration with her new health care provider to help assure that they will continue to receive the careful monitoring that they need to optimize adult health and longevity.

Psychological and Educational Issues

Cognitive and educational performance

The majority of individuals with TS have normal intelligence, although patients with a small ring X-chromosome clearly have an increased risk of mental retardation (122). These individuals may have a severe phenotype with features atypical for TS, apparently due to failure of small rings to inactivate (123). Individuals with TS have an increased risk for a selective impairment in nonverbal skills and, as a group, score lower on performance than on verbal subsections of standardized intelligence tests (124). In school, these impairments are manifested as math, visuospatial, and executive function deficits (125). Slowed response time is observed across each of these three domains (126). The specific neuropsychological deficits include four interacting areas of functioning: visual-spatial organization deficits (*e.g.* difficulty with direction sense), difficulty with social cognition (*e.g.* failure to appreciate subtle social cues), difficulty with problem solving (*e.g.* mathematics), and motor deficits (124, 126–128). Some of these deficits may be improved by hormonal therapy at the time of puberty (129). A higher than expected rate of attention deficit disorder diagnoses (*i.e.* 24%) is reported in school-age girls (130). Drawing from the broader field of educational research, it is possible that educational intervention directed at learning or attentional difficulties may offer additional benefits. Despite variable degrees and areas of learning difficulties, as a group, girls and women with TS excel at verbal skills and many adults with TS have university-level education (131–133).

Psychological development

Overall, behavioral function is normal in girls with TS. However, there may be an increased risk for social isolation, immaturity, and anxiety (134, 135).

Girls with TS typically have a female pattern of gender identity, but adolescent and adult women with TS achieve sexual milestones later than their peers and are less likely to marry (136, 137). It is unclear whether this delayed sexual activity reflects some underlying genetic or hormonal influence on behavior or the timing of puberty. Recent studies do not support the influence of height (137, 138) as influential on dating and initiation of sexual activities, but the role of physical anomalies is unclear. The developmental process is likely affected by treatments with GH and estrogen that potentially influence the child's perception of herself.

Psychosocial function in adults with TS

Young, GH-treated adults on average have normal self-perceived physical and mental health, but some women experience decreased self-esteem, mostly in the context of social functioning (139). Adult height does not appear to impact adult quality of life (117, 139). Formal psychiatric evaluation of 100 adult volunteers with TS participating in a National Institutes of Health natural history study revealed no increase in major psychiatric diagnoses other than depression and anxiety-related disorders, which were higher than those reported from a community-based sample but similar to those reported in women from a general gynecological clinic sample (140). Women with TS report significantly higher levels of shyness and social anxiety and reduced self-esteem compared with normal menstruating women but similar to karyotypically normal women with premature ovarian failure, suggesting that the experience of ovarian failure and infertility contribute to psychosocial dysfunction (138). Supporting this view, these same women with TS reported in open-ended interviews that dealing with premature ovarian

failure and loss of fertility was the most difficult part of having TS (18).

Recommendations

Significant psychosocial risks are associated with TS, including cognitive, social, and behavioral components. Plans for both medical and psychological intervention should be developed so as to reinforce and support the individual's self-esteem and to ensure that individuals remain in the mainstream of social, educational, and employment activities. Many of these issues are discussed in patient-oriented material available through the Turner Syndrome Society of the United States (www.turner-syndrome-us.org) and from other local and national TS organizations (*e.g.* Magic Foundation, www.magicfoundation.org). Early involvement in a TS support group should be encouraged.

A comprehensive psycho-educational evaluation is recommended immediately preceding school entry or at the time of TS diagnosis. Evaluations may need to be repeated during primary school if indicators of academic difficulties emerge. Children with TS may also have other conditions; as for all children, if evidence of other difficulties emerge (such as dyslexia or attention deficit), evaluation and treatment should be encouraged. As with documentation of learning disability in any child, classroom accommodations and modifications may be necessary and could be considered at any age as needed. For example, in view of the slower processing speeds observed in girls with TS, untimed testing may be appropriate. In many cases, it may be useful to refer children and their families to educational specialists to facilitate development of coping strategies, such as reliance on relatively superior verbal skills to mediate problem solving. In childhood, parents should be alerted to possible peer issues and educated about strategies to deal with difficulties such as social isolation.

Age-appropriate pubertal induction is recommended because of potential long-lasting psychosocial implications of delayed pubertal development. Discussions should be initiated regarding sexuality and reproductive options at age-appropriate levels. It is sometimes difficult for adult caregivers to address the ramifications of a TS diagnosis, especially infertility. However, it is important to address these issues in an honest and open manner, because secret-keeping may have unintended negative consequences and actually amplify the problems for girls and young women (141). Age-appropriate social interactions should be encouraged. Finally, attention should be given to career and vocational planning and preparation for transition to living independently, starting in adolescence. Learning disabilities can be a major impediment to emancipation from family and to career enhancement, although many women with TS do achieve high professional status.

Medical Care for Adults with TS

Medical follow-up and estrogen replacement therapy

Adult women with TS require careful medical follow-up. Early medical intervention may decrease the substantially increased morbidity (142, 143) and mortality (144, 145) and improve the quality of life of women with TS. Ideally, the process of transition should take place over a period of 2–3 yr during the late pubertal period as described above and should involve an adult endocrinologist and a gynecologist with expertise in premature ovarian failure. A multidisciplinary team including specialists in endocrinology, cardiology, hearing and ear-nose-throat, infertility/gynecology, and psychology may be developed at a tertiary care center. The agenda for such a specialist service should be developed in partnership between medical professionals and Turner support groups. Regrettably, late diagnosis of TS, even in adults, is still a problem. No matter what the age of the patient, a full workup with assessment of congenital malformations should be performed, including all screening tests recommended for younger patients (Table 2).

Upon transfer to an adult care clinic, the young woman with TS should undergo a comprehensive medical evaluation, addressing not only the specific problems associated with TS but also screening for osteoporosis, hypertension, diabetes, and dyslipidemia, which are increased in TS (143). All medical problems present during childhood should be followed in adults, especially congenital cardiovascular issues, thyroid and celiac disease, and hearing loss (Table 3). Annual medical history and general physical evaluation should be performed, including blood pressure, heart auscultation, clinical evaluation of thyroid size and function, breast examination, and Pap smear. As in children, regular otological examination is important, because about 60% of adults with TS experience senorineural hearing loss. The hearing loss is progressive but tends to occur more rapidly after about 35 yr of age, leading to early presbyacusis (146). Hearing aids are frequently necessary. Otological screening should be conducted at least every 2–3 yr in patients who are asymptomatic and have previous documented normal hearing and more frequently as indicated for those with established hearing loss or new symptoms of hearing loss.

Many of the problems of adult life in patients with TS are compounded by obesity (147, 148), partly because of low physical fitness and a sedentary lifestyle (149, 150). Lifestyle education with advice on diet and exercise must be included in a program of prevention of diabetes, osteoporosis, and hypertension. Women with TS should aim to have a body mass index less than 25 kg/m^2 and a waist/hip ratio less than 0.80. Any exercise program should be developed with consideration of individual skeletal or cardiovascular problems, and a physical rehabilitation specialist or trainer may be of great value in designing individualized programs for patients with physical limitations.

Laboratory tests

Laboratory testing of women with TS should be carried out at 1- to 2-yr intervals and include measurements of usual screening tests, such as hemoglobin, white blood cell count, renal function (creatinine and blood urea nitrogen), but should especially include fasting blood glucose lipid profile, liver enzymes, TSH, and total or free T_4.

Recommendations for breast evaluation, self-examination, and mammography are the same as for the general population.

Hepatic disease

Liver enzymes, especially γ-glutamyl transferase, alanine amino transferase, aspartate amino transferase, and alkaline phosphatase, are commonly raised in women with TS, but their relationship to chronic liver disease is unknown (148, 151). Hepatitis serology can be checked if indicated, although the prevalence of viral hepatitis is not raised in TS. Usually, elevated liver enzymes do not progress to overt hepatic disease, but regenerative nodular hyperplasia and other architectural abnormalities or biliary lesions are seen on biopsy, as is portal hypertension, which should be treated according to hepatology guidelines (152). Estrogen treatment is not associated with adverse effects on the liver and usually lowers liver enzymes in TS and thus is not contraindicated in patients that have elevated liver enzymes (151). If elevated liver enzymes persist for more than 6–12 months, an ultrasound should be performed to rule out hepatic steatosis. If steatosis is not present and liver enzymes remain elevated or increase, a hepatology consult may be obtained with consideration of biopsy guided by the use of hepatic ultrasound with assessment of blood flow by Doppler. Potentially hepatoxic drugs such as statins and glitazones have to be prescribed with caution in affected patients.

Renal function

Although congenital structural anomalies of the kidney are found in about 30% of TS patients, renal function is usually normal, with the only common complication being urinary infections related to obstruction. Thus, individuals with known renal collecting-system anomalies may require more frequent screening for urinary tract infections.

Bone metabolism

Fractures are increased in older patients with TS, but these patients may not have received optimal estrogen treatment in the past. Most studies using dual-energy x-ray absorptiometry find decreased bone mineral density (BMD) (149, 153), but small size may lead to underestimation of BMD by dual-energy x-ray absorptiometry (154). When adjusted for size, women that have received appropriate estrogen treatment usually have normal BMD in trabecular bone, *e.g.* the spine (149, 154). However, there seems to be an intrinsic, estrogen-independent deficit in cortical bone in TS (149, 155, 156). A baseline BMD should be obtained at the initial visit in the adult clinic, with follow-up depending on the initial result. If the BMD is normal (adjusting for size), additional evaluation need not take place until age 40–50 yr or when the patient plans to discontinue estrogen treatment. If BMD is low in a young woman with TS, one needs to investigate and treat possible contributory factors such estrogen replacement noncompliance, tobacco use, excessive alcohol use, possible celiac disease, or vitamin D deficiency. Proper estrogen treatment improves BMD and is the mainstay of bone protection. Adequate calcium and vitamin D intake is essential, because many women have low levels of vitamin D. Weight-bearing exercise is very important in achieving and maintaining BMD and should be encouraged.

Bisphosphonates or other antiosteoporotic pharmaceuticals are not recommended for treating osteopenia in young women with TS, because reduced cortical BMD in TS is not proven to lead to increased fractures and bisphosphonates have not been shown to be effective in enhancing cortical BMD in TS. Furthermore, these agents may blunt treatment with newer modalities in the future and are contraindicated in women who might attempt pregnancy. For women with confirmed osteoporosis, especially those at risk for fracture, or who have already sustained a low-impact fracture, the usual medical treatment for osteoporosis is indicated.

Risk factors for coronary artery disease

In addition to their burden of congenital cardiovascular disease, women with TS are at increased risk for atherosclerosis. Hypertension affects as many as 50% of young adult patients. Blood pressure should therefore be closely monitored and hypertension treated vigorously (57, 63, 150). Increased heart rate and altered autonomic innervation of the heart are common in TS (54). Type 2 diabetes is common in TS. An oral glucose tolerance test uncovers impaired glucose tolerance or diabetes in more than 50% of cases, usually associated with an insulin secretory defect in TS (57, 157). Insulin sensitivity may be normal in many patients but reduced in those with obesity or a strong family history of type 2 diabetes. Often, the diabetes is relatively mild and responsive to weight loss or monotherapy.

Low-density lipoprotein cholesterol and triglycerides are elevated, and lipid particle size is reduced in women with TS compared with age and body-mass-index-matched women with karyotypically normal ovarian failure (158, 159), suggesting that the X chromosome deletion *per se*, apart from the effects of premature ovarian failure, is associated with dyslipidemia.

Thyroid and celiac disease

As indicated in the pediatrics section, screening for thyroid and celiac diseases may continue throughout adult life (Table 3) because of an increased risk of developing overt disease (82).

Ovarian hormone replacement

It is recommended that women with TS receive cyclical estrogen and progestin. Sufficient estrogen should be prescribed to prevent the symptoms, signs, and sequelae of estrogen deficiency. An estrogen dose equivalent to 2 mg estradiol daily suffices for most adult women with TS, but individual requirements may vary from 1–4 mg/d. Ideally, natural estradiol and progesterone, rather than analogs, should be delivered by transdermal or transmembranous routes so as to mimic age-appropriate physiological patterns as closely as possible. However, regimens that meet each individual woman's tolerance and preference vary widely, and the most important consideration is that women actually take ovarian hormone replacement. This is critical because the risk of clinically significant osteoporosis with spontaneous fractures is very high in young women with TS not taking estrogen (132). As with other women receiving estrogen replacement therapy, pelvic ultrasonography and endometrial

biopsy should be considered when abnormal vaginal bleeding occurs. Androgen concentrations are reduced in many women with TS (160), and androgen substitution therapy may be of value in some instances. This is an area that needs additional investigation. The duration of estrogen therapy should be individualized, and readjustment of dosage or discontinuation should occur at the age of normal menopause.

Fertility and family-planning issues

Although a few patients with TS achieve spontaneous pregnancy, most are infertile. Various assisted reproductive techniques are now available for achieving pregnancy. Recent studies show that women with TS become pregnant as easily as women with other types of infertility and carry their pregnancies to term without an increased miscarriage rate (161, 162); however, they do have an increased rate of maternal complications (65). First, because of their small size, many women with TS need to deliver by cesarean section. Second, hypertension and diabetes are common in TS pregnancy (162). Most critically, the risk for dilatation and dissection of the aorta appears to increase during pregnancy (65). Karnis *et al.* (65) also found that only approximately 50% of women in the United States had a cardiac workup before fertility treatment. Before contemplating spontaneous or assisted pregnancy, individuals with TS need a complete medical evaluation. Particular attention should be paid to the cardiovascular system, and echocardiography, ECG, and MRI need to be performed before any attempt at pregnancy. Women with cardiovascular issues (BAV, dilated aorta, or history of coarctation), as described above, are best counseled against attempted pregnancy (163). In addition, thyroid status and glucose tolerance should be monitored. All pregnancies should be followed by a multidisciplinary team, including high-risk pregnancy specialists, endocrinologists, and cardiologists, generally at a tertiary care facility.

Women with functional ovaries

Women with TS who have spontaneous menstrual cycles and ovulate normally should receive counseling on the timing of pregnancies: because of the risk of premature ovarian failure, pregnancies should not be postponed without good reason, and the possibility of oocyte or embryo cryopreservation; the risk of miscarriage and chromosomal abnormalities in the offspring; and the possibility of prenatal genetic testing.

Women without functional ovaries

Oocyte or embryo donation can be used to achieve pregnancy in patients with TS who do not have functional ovaries (161). Special attention should be given to appropriate preparation of the uterus. This requires adequate hormone replacement therapy for 1–2 yr before oocyte or embryo transfer to increase the size of and improve the blood flow in the uterus. Adequate uterine preparation has to be performed (4, 6, or 8 mg of 17β-estradiol and a gestagen), and optimally, the thickness of the endometrium should be 7 mm. Ideally, only one embryo should be transferred at a time to avoid the additional risks associated with multiple pregnancies. An embryo cryopreservation program is therefore essential. Under optimal conditions, spontaneous vaginal delivery is an acceptable option. Cesarean section, however, is often employed because of a narrow pelvis. Adoption is an option for many women with TS, and the use of surrogate mothers is an option in some countries.

Cryopreservation of ovarian tissue and immature oocytes

New data have emerged during the last years showing that adolescents with only few signs of spontaneous puberty may still have ovaries with follicles (28). The possibility of using cryopreserved ovarian tissue and immature oocytes, obtained before regression of the ovaries occurs in childhood, is currently under intensive investigation, and results seem promising (28). Although only a research tool at present, this technique may provide the possibility of pregnancy with the patient's own oocytes.

Summary

This consensus statement arose from an interdisciplinary meeting of geneticists, pediatricians, cardiologists, internists, behavioral health specialists, and gynecologists involved with the care of and clinical research on patients with TS. Our goal was to address new information and experience that has accrued in the past 5–6 yr since the last international workshop with regard to practical implications for the diagnosis and care of individuals with TS. The first issue was the high elective abortion rate for incidentally diagnosed 45,X and 45,X/mosaic fetuses (14, 15), which seemed at odds with recent reports of a normal quality of life for individuals receiving current medical care (117, 131, 133). Another paper reviewing care for individuals with TS, in general agreement with this article, has appeared during the review process (165). It was clear that the content of prenatal counseling on the significance of such a karyotype for expectant parents needs updating and needs inclusion of TS patient and parent groups. Participants were in favor of the initiation of newborn screening for TS, with the caveat that a suitable infrastructure to provide educational and psychological support for families must be established. An expanded view of congenital cardiovascular disease in TS led to the recommendation for diagnostic cardiovascular MRI study for all patients and increased focus on regular monitoring of systemic blood pressure and aortic diameter in children and adults. Concerns have been raised about cardiovascular risks associated with pregnancy in TS and inadequate medical evaluation before conception (163), hence new cautions for individuals with existing cardiovascular issues. GH treatment has now been proven to increase adult height (98), although whether this effect confers an advantage to adults with TS has not been proven (117). Because growth appears to continue apace with the gradual introduction of estradiol, pubertal development generally should not be delayed to further increase adult height. Pubertal delay may exacerbate the negative psychosocial impact of early ovarian failure, associated with excessive shyness and social anxiety, delayed sexual debut, and decreased marriage rate. The increased frequency of nonverbal learning and attention deficit disor-

ders in girls with TS mandates comprehensive testing at an early age so as to implement appropriate educational plans in a timely manner. The care of adults with TS has received less attention than the treatment of children, and many seem to be falling through the cracks with inadequate cardiovascular evaluation (166) and estrogen treatment (167).

Last, it is important to recognize that the recommendations in this document are based on the authors' best judgments given the current level of medical knowledge. There are many questions that remain unanswered regarding care for girls and women with TS, such as identifying the optimal age of initiation and duration of GH treatment, specific interventions for attention and perceptual deficits, the best method of ovarian hormone replacement across the lifespan, and the most effective monitoring for osteoporosis and cardiovascular disease.

Acknowledgments

* The Turner Syndrome Consensus Study Group includes the following: Carolyn Bondy, M.D., Conference and Writing Committee Chair, Developmental Endocrinology Branch, National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH); Neus Baena, M.D., Genetics Laboratory, Corporacio Sanitaria Parc Tauli, Institut Universitari Parc Tauli-UAB, Sabadell, Spain; Vladimir K. Bakalov, M.D., Developmental Endocrinology Branch, NICHD, NIH; Barbara Bowles Biesecker, M.S., National Human Genome Research Institute, NIH; Jean-Claude Carel, M.D., Endocrinologie Diabétologie Pédiatrique and Institut National de la Santé et de la Recherche Médicale U690, Hôpital Robert Debré, Paris, France; Gerard Conway, M.D., Department of Endocrinology, Middlesex Hospital, Mortimer Street, London, UK; Marsha Davenport, M.D., Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC; Christine Disteche, Ph.D., Department of Pathology and Medicine, University of Washington, Seattle, WA; Megan Freebury Karnis, M.D., FRSCS, Division of Reproductive Endocrinology and Infertility, McMaster University, Hamilton, Ontario, Canada; John A. Germak, M.D., Novo Nordisk Inc., Princeton, NJ; Claus H. Gravholt, Ph.D., M.D., Medical Department M (Endocrinology and Diabetes), Aarhus Sygehus, Aarhus University Hospital, Aarhus, Denmark; Joanne Foodim, M.D., New Haven, CT; Daniel Gunther, M.D., Department of Pediatrics and Endocrinology, Children's Hospital and Regional Medical Center, Seattle, WA; Outi Hovatta, M.D., Division of Obstetrics and Gynaecology, Karolinska Institute, Huddinge University Hospital, Stockholm, Sweden; Anne-Marie Kappelgard, M.D., Novo-Nordisk A/S; Wieland Kiess, M.D., Hospital for Children and Adolescents, University of Leipzig, Leipzig, Germany; Kerstin Landin-Wilhelmsen, M.D., Endocrine Division, Sahlgrenska University Hospital, Goteborg, Sweden; Angela Lin, M.D., Genetics and Teratology Unit, Massachusetts General Hospital for Children, Boston, MA; Barbara Lippe, M.D., Genentech; Melissa Loscalzo, M.D., University of South Florida, All Children's Hospital, St. Petersburg, FL; Kelly Lynch, M.D., Baystate Medical Center, Springfield, MA; Laura Mazzanti, M.D., Department of Pediatrics, Pediatric Clinic, S. Orsola-Malpighi Hospital, Bologna, Italy; Michèle M. M. Mazzocco, Ph.D., Johns Hopkins School of Medicine, Baltimore, MD; Elizabeth McCauley, Department of Psychiatry, University of Washington/Children's Hospital and Medical Center, Seattle, WA; Paul McDonough, M.D., Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta, GA; Sabine M. P. F. de Muinck Keizer-Schrama, M.D., Department of Pediatrics, Sophia Children's Hospital/Erasmus MC, Rotterdam, The Netherlands; Rune Weis Naeraa, M.D., Pediatric Department, Randers Central Hospital, Randers, Denmark; Charmian Quigley, M.D., Eli Lilly & Co., Indianapolis, IN; Robert Rosenfield, M.D., University of Chicago Children's Hospital, Chicago, IL; Douglas Rosing, M.D., National Heart, Lung, and Blood Institute, NIH, Bethesda, MD; Judy Ross, M.D., Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA; Dominique Roulot, M.D., Service d'Hepato-gastroenterologie, Hopital Jean Verdier, Bondy, France; Karen Rubin, M.D., Division of Pediatric Endocrinology, University of Connecticut School of Medicine, Farmington, CT; Paul Saenger, M.D., Department of Pediatrics, Montefiore Medical Center, Bronx, NY; Peter Schmidt, M.D., National Institute of Mental Health, Bethesda, MD; Mike Silberbach, M.D., Doernbecher Children's Hospital, Portland, OR; Virginia Sybert, M.D., Division of Dermatology, University of Washington School of Medicine, Seattle, WA; Daniel L. Van Dyke, Ph.D., Mayo Clinic, Rochester, MN; and Andrew Zinn, M.D., Ph.D., McDermott Center for Human Growth and Development and Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX.

Section Chair or Cochairs were Andrew Zinn, Genetics; Mike Silberbach and Angela Lin, Cardiology; Marsha Davenport, Growth and Development; Judy Ross, Psychosocial and Educational Development; and Gerard Conway and Claus H. Gravholt, Adult and Gynecological Care.

We thank Duane Alexander, M.D., Director, NICHD, for his faithful support of research aimed at improving the lives of girls and women with TS. We appreciate the generous participation in clinical research by families of girls with TS and girls and women with TS. We acknowledge expert advice from Alan DeCherney, M.D., NICHD, NIH; Harry Dietz, M.D., Johns Hopkins, Baltimore, MD; Andrew Griffith, National Institute of Deafness and Other Communication Disorders, NIH; Vincent Ho, M.D., Uniformed Services University of the Health Sciences and NIH Clinical Center, Bethesda, MD; and Jacquelyn Noonan, M.D., University of Kentucky. We acknowledge the support for the Wellness for Girls and Women with Turner Syndrome Conference generously provided by the National Institute of Child Health, Genentech, Eli Lilly, Novo-Nordisk, and Pfizer.

Received June 27, 2006. Accepted October 6, 2006.

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This work is based on the proceedings of an international, multidisciplinary meeting, "Wellness for Girls and Women with Turner Syndrome," sponsored by the National Institute of Child Health, Bethesda, Maryland, April 6–9, 2006.

Disclosure: C.A.B. has nothing to disclose.

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JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Laboratory guideline for Turner syndrome

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Disclaimer: This guideline is designed primarily as an educational resource for health care providers to help them provide quality medical genetic services. Adherence to this guideline does not necessarily ensure a successful medical outcome. This guideline should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the geneticist should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from this guideline.

Abstract: Turner syndrome is a disorder that has distinct clinical features and has karyotypic aberrations with loss of critical regions of the X chromosome. Several clinical guidelines on the diagnosis and management of patients with Turner syndrome have been published, but there is relatively little on the laboratory aspects associated with this disorder. This disease-specific laboratory guideline provides laboratory guidance for the diagnosis/study of patients with Turner syndrome and its variants. Because the diagnosis of Turner syndrome involves both a clinical and laboratory component, both sets of guidelines are required for the provision of optimal care for patients with Turner syndrome. ***Genet Med* 2010:12(1):52–55.**

Key Words: *Turner syndrome, guideline, cytogenetics, mosaicism*

Although clinical guidelines have addressed diagnosis of Turner syndrome,[1–5] laboratory guidelines are lacking. This American College of Medical Genetics (ACMG) laboratory guideline provides information on appropriate pre- and postnatal diagnostic cytogenetic studies for Turner syndrome. Disease-specific statements are intended to augment the current general ACMG Standards and Guidelines for Clinical Genetics Laboratories. Individual laboratories are responsible for meeting the Clinical Laboratory Improvement Amendments/College of American Pathologists quality assurance (QA) standards with respect to appropriate sample documentation, assay validation, general proficiency, and quality control measures.

This guideline is based on peer-reviewed scientific literature to the extent possible. However, there are relatively few articles published on laboratory practice for Turner syndrome, and hence expert consensus opinion was elicited to obtain best practices. The guideline was reviewed extensively by select experts on Turner syndrome, including Cytogeneticists and Clinical Geneticists, the ACMG Cytogenetic subcommittee of the Laboratory QA Committee, the QA Committee, and the ACMG Board of Directors. In addition, the document was vetted by the entire ACMG membership before adoption as a supplement to the ACMG Laboratory Standards and Guidelines.

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Disclosure: The authors declare no conflict of interest.

Submitted for publication October 16, 2009.

Accepted for publication October 16, 2009.

DOI: 10.1097/GIM.0b013e3181c684b2

BACKGROUND ON TURNER SYNDROME

Chromosome locus

A majority of genes associated with the physical features observed in Turner syndrome are located on Xp (Xp11.2-p22)[6]; loci contributing to ovarian function reside in Xq (Xq24).[7]

Disease incidence and karyotypic finding

The disease incidence is approximately 1 in 2500 liveborn females. A 45,X karyotype is observed in ~1% to 2% of conceptuses, 10% of miscarriages and 1% of stillbirths. Greater than 99% of 45,X conceptuses result in spontaneous loss, usually before 28 weeks. The reason why ~1% survive to term with relatively minor somatic abnormalities is not known, although it has been hypothesized that this is due to undetected mosaicism for a cell line with all or part of a second sex chromosome.[8,9]

Karyotype findings associated with Turner syndrome

Prenatal. Approximately 1% to 2% of conceptuses have a 45,X karyotype. These fetuses typically have ultrasound findings such as cystic hygroma or nuchal thickening. A majority of cases with mosaicism for a 45,X cell line and a cell line with a second structurally normal sex chromosome result in the birth of a child with a normal phenotype.[10,11]

Postnatal. Apparently nonmosaic monosomy X is found in ~45% of patients with Turner syndrome postnatally. A structural chromosome abnormality or mosaicism for 45,X and another cell line is found in the lymphocytes of the remaining patients with Turner syndrome (Table 1).

Table 1 Turner syndrome karyotypes

Karyotype	Percentage of TS cases[12–14] (%)
45,X	45
46,X,i(X)(q10) w/ or w/o 45,X	15–18
46,X,+mar or +r w/ or w/o 45,X	7–16
45,X/46,XX or 45,X/47,XXX	7–16
46,X,del(Xp) w/ or w/o 45,X	2–5
46,XY or 46,X,del(Y) or 46,X,r(Y) w/ 45,X	6–11
Others	2–8

Brief clinical description

The features of Turner syndrome include characteristic physical features and complete or partial absence of the second sex chromosome. Phenotypic features vary widely but commonly include short stature, ovarian failure, edema of hands or feet, nuchal folds, left-sided cardiac anomalies, low hairline, low set ears, small mandible, cubitus valgus, nail hypoplasia, hyperconvex nails, multiple pigmented nevi, characteristic facies, short fourth metacarpal, and high arched palate. Females with short stature and deletion of the distal region of Xp including the *SHOX* gene are generally not diagnosed with Turner syndrome. Likewise, individuals with deletions of Xq24 with primary or secondary amenorrhea without short stature are typically diagnosed with premature ovarian failure.[15]

Mode of inheritance

Turner syndrome is sporadic. A majority of cases ascertained prenatally have a 45,X karyotype. Paternal nondisjunction accounts for ~70% of liveborn cases with a 45,X.[16–17]

Ethnic association

Turner syndrome is seen in all ethnic groups.

Special testing considerations

A differential diagnosis that includes Turner syndrome must take into consideration phenotypic features in combination with karyotypic findings. The phenotype varies greatly, therefore, both laboratory and clinical factors must be considered before a diagnosis may be rendered. Mental retardation is not a feature of Turner syndrome. The only sex chromosome structural abnormalities likely to cause mental retardation are a ring X chromosome with loss of *XIST* gene function and certain X-autosome translocations.

Presence of Y chromosome material

Mosaicism for a cell line with a normal or abnormal Y chromosome is identified in 6% to 11% of patients with Turner syndrome with standard cytogenetic techniques. Identification of Y chromosome material in females with Turner syndrome is important because of the risk of gonadoblastoma.[18] A gonadoblastoma is a neoplasm composed of germ cells and sex cord elements with an excellent prognosis if detected early. However, gonadoblastoma can progress to dysgerminoma with metastatic potential. A gonadoblastoma-susceptibility locus has been proposed for the pericentromeric region of the Y chromosome.[19–20] The neoplasm does not appear to correlate with the presence of *SRY*.

Occult Y chromosome mosaicism detected by techniques other than standard cytogenetics in Turner syndrome varies by study and with methodology used.[13,21–25] A meta-analysis of studies reporting a total of 541 patients with Turner syndrome without Y chromosome material on routine cytogenetic analysis found 5% mosaicism for a Y-containing cell line using molecular techniques (Southern blot and/or polymerase chain reaction [PCR]). The percentage of patients with Y chromosome mosaicism (by molecular or standard cytogenetic techniques) was 8%, and, of these, 12% had gonadoblastoma. Detection of occult Y mosaicism in 45,X subjects using interphase fluorescent in situ hybridization (FISH) with a probe for the Y centromere (DYZ3) has been reported to range from 0% to 4%.[24,25]

Prenatal testing

Monosomy X is frequently identified by prenatal diagnostic procedures. Ultrasound findings can include nuchal translucency, cystic hygroma, coarctation of the aorta and/or other left-sided heart defects, brachycephaly, renal anomalies, polyhydramnios, oligohydramnios, and growth retardation. Abnormal prenatal serum marker screening results with elevated levels of human chorionic gonadotropin and inhibin and slightly decreased levels of alpha fetoprotein and unconjugated estriol are associated with an increased likelihood of a Turner syndrome diagnosis.[27,28] Prenatal diagnosis may indicate a karyotype consistent with a diagnosis of Turner syndrome; however, the phenotype of the individual cannot be predicted based on the chorionic villus or amniotic fluid cell karyotype, FISH, or microarray results. In the absence of abnormal prenatal ultrasound findings, girls with incidental prenatal karyotype findings associated with Turner syndrome have a less severe phenotype with fewer physical abnormalities compared with those diagnosed due to abnormal ultrasound findings. Because the constitutional karyotype of individuals with prenatal ascertainment of sex chromosome complements consistent with Turner syndrome is uncertain, postnatal chromosome studies are recommended. Failure to confirm the prenatal findings with a blood karyotype should prompt consideration of analysis of another tissue such as buccal or skin cells.

Females with monosomy X or a structurally abnormal X chromosome may manifest X-linked recessive disorders; when an X-linked recessive disorder is identified in a female, karyotyping is warranted.

The detection of a low level of 45,X cells (<10%) during routine cytogenetic analysis of peripheral blood or bone marrow from an adult female can be difficult to interpret. It has been well documented that there is age-related loss of the X chromosome.[29] Laboratories should have procedures for an evaluation that assists with the determination of the significance of 45,X cells detected in women based on age, and for reporting, when appropriate.

GUIDELINE

Methodological considerations

Prenatal diagnosis

Refer to the ACMG Laboratory Standards and Guidelines (www.acmg.net, 2008) for general laboratory recommendations on prenatal diagnosis.

When multiple cells from a single culture are identified with a 45,X karyotype, a moderate work-up is warranted. This includes examination of an additional 20 cells from cultures other than the one with the initial finding or 12 colonies from coverslips other than the one with the abnormality.[30]

Additional cells or colonies should be evaluated when a structurally abnormal X chromosome is identified to determine if the finding is true or pseudomosaicism. Depending on the aberration (e.g., marker chromosome and unbalanced or balanced structural abnormality in single or multiple cultures), guidelines for moderate or extensive evaluation would apply.[30]

When an apparent sex chromosome marker is identified in a fetus with only a single X chromosome, a moderate (if found in a single cell in culture or on a single coverslip) or extensive work-up (if found in multiple cells in a single culture or multiple colonies from a single coverslip) is recommended.[30]

If the marker is found in every cell or is mosaic, additional testing to identify the origin of the marker using FISH with X and Y centromere probes is recommended.

When a small ring or small marker chromosome is determined to be derived from the X chromosome, FISH with a probe for the XIST gene should be performed. Depending on the size and content of the small ring/marker, lack of the *XIST* locus may be associated with a more severe phenotype that includes mental retardation.[26,31]

For interphase analysis using X and Y centromere probes, normal cutoff values should be established for a second X chromosome signal using normal male controls, and for a Y chromosome signal using normal female controls.[25] See section E10 for information on establishment of a normal cut-off value (ACMG Standards and Guidelines, www.acmg.net, 2008).

Postnatal studies

Cases being studied for possible Turner syndrome, in which mosaicism is common, should include a minimum of 30 cells counted, unless mosaicism is documented within the first 20 cells. When low-level mosaicism for 45,X is detected, the age of the female should be taken into consideration to ensure that the 45,X cell line is not due to age-related loss.[29]

Cytogenetic study of a second tissue (e.g., skin biopsy for cell culture or buccal smear for FISH) should be considered in individuals with a 46,XX karyotype only if there is a high level of suspicion for Turner syndrome based on phenotype. Consultation with the referring physician is recommended to determine whether a second tissue should be studied.

Additional studies are warranted if a 30-cell analysis reveals an apparently nonmosaic 45,X karyotype. In patients without virilizing features with a nonmosaic 45,X karyotype, FISH analysis using X and Y probes can identify low-level sex chromosome mosaicism.[25] Although the frequency of gonadoblastoma in Turner syndrome with occult Y chromosome mosaicism without evidence of virilization is not fully appreciated, additional studies are recommended in these cases to help prevent a potential life-threatening cancer.[32]

FISH with X and Y centromere probes should be performed on a minimum of 200 interphase cells. An appropriate database should be created and normal cutoff values should be established for a Y chromosome signal using normal female controls.[25] See section E.10 for information on establishment of a normal cutoff value (ACMG Standards and Guidelines, www. acmg.net, 2008).

If the patient reveals an apparently nonmosaic 45,X karyotype and has clitoromegaly or other masculinizing features, it is very likely that there is mosaicism for a Y chromosome-containing cell line.[15] FISH with probes for the X and Y centromeres should be performed on a minimum of 200 cells to detect low-level Y chromosome mosaicism. Given the high suspicion for Y chromosome material, study of a second cell type may be warranted. Consultation with the referring physician is recommended.

Additional studies should be performed when a small ring/marker chromosome is identified. This is the same as for section "Prenatal Diagnosis" earlier. Note that there is not always a correlation between the presence of *XIST* in the ring and cognitive phenotype.[33] The size of the active ring appears to have a greater correlation with outcome.[34–36]

Interpretation and reporting

The following elements should be included in the report, in addition to the items described in the current general Standards and Guidelines.

Referral for genetic counseling and evaluation by a clinical geneticist and/or other appropriate health care provider.[15,37]

When a karyotype consistent with Turner syndrome is found prenatally, postnatal chromosome analysis is recommended to document the child's karyotype.[38]

ALTERNATIVE TESTING METHODS

PCR

For detection of Y-chromosomal material using PCR, a high rate of false-positive results has been reported.[25,39] Thus, caution should be exercised in the interpretation of Y-chromosome sequence PCR. FISH confirmation using a Y centromere probe after a positive PCR result is prudent.

Genomic copy number microarray studies can be used to further characterize abnormalities that are detected by cytogenetic studies. However, microarrays may not detect low-level mosaicism and should not be used as the initial screen for sex chromosome abnormalities.

ACKNOWLEDGMENTS

The authors thank Virginia Proud and the Professional Practice and Guidelines Committee Chairs, Rick Martin and Helga Toriello, for their input on the clinical significance of laboratory findings associated with Turner syndrome.

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ПедиатриЯ

ISSN 0479-7876 ТОМ L, 2010 г.

Издава Българска Педиатрична Асоциация

Включена в Excerpta Medica Database EMBASE

Адрес на редакцията:
София 1606
бул. „Акад. Ив. Гешов“ № 11

Публикуваните в списанието фигури са авторски оригинали.

СЪДЪРЖАНИЕ

Рекомбинантен човешки растежен хормон в комбинация с малки дози естрогени стимулират растежа и пубертетното развитие при момичета със синдром на Turner

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Ключови думи: *Синдром на Turner, Лечение с rhGH, Етиология и патогенеза на синдром на Turner.*

Двата централни симптома при синдрома на Turner са изоставането в растежа и хипергонадотропния хипогонадизъм с инфертилитет, дължащ се на гонадна дисгенезия и овариална хипофункция. Към това се описват редица дисморфични белези и малформации - вродени сърдечни пороци, артериална хипертония, вродени бъбречни малформации, скелетни малформации, характерни лицеви аномалии, къса шия и pterygium coli, кожни симптоми. Съобщават се висока честота на автоимунни заболявания, нарушения във въглехидратната и липидна обмяна и редица психологични проблеми.

Етиологията и патогенезата на синдрома и отчасти необяснимата комбинация от симптоми се изясни постепенно през последните години (25,31,37,50). Основната причина е пълна или частична липса на едната Х-хромозома във всички клетки на тялото, като в 70%-75% от случаите останалата Х-хромозома е майчина (18). Множество гени, разположени на късото рамо на Х-хромозомата са определящи фактори за нормалния растеж, овариалната структура и структурата на други органи

Най-често, в 50%-60%, е комбинацията 45Х, при която има сърдечни и бъбречни малформации и лимфедем (12). Данни за материал на У-хромозома се откриват в 5%-10% от пациентките. Такива случаи има клинични белези на вирилизация (2).

Вариациите в хромозомните комбинации са представени в **табл. 1.**

Вариабилността на клиничните симптоми се обяснява с различната инактивация на Х-хромозомата и отпадане активността на гени, експресирани там - за растежа, за развитието та яйчниците, за познавателната способност и др. (16, 25, 31, 37, 49, 50).

Повечето автори смятат, че изоставането в растежа, гонадната дисгенезия и другите аномалии са резултат на отделни генетични дефекти. Според Zinn (1998) е трудно да се идентифицират специфичните гени, отговорни за отделните симптоми, тъй като Х-хромозомата кодира голям брой гени. Предизвикателство е, обаче да се търси кои от тези гени, действащи сами или в комбинация, са отговорни за определяне фенотипа на синдрома на Turner (49).

Честотата на синдрома е от 1:2000 до 1: 2500 живородени момичета (2).

Ниският ръст при синдрома на Търнер е един от най-честите симптоми. Среща се в 80% - 100%. Той се дължи на интраутеринно изоставане в растежа, намалена растежна скорост след раждането и липсата на пубертетен растежен скок. Ниският ръст, скелетните и краниофациалните аномалии се свързват с дефицит или липса на т.нар. SHOX- ген (short stature homeobox containing gene on X- chromosome).Той е локализиран на терминалния край на двете Х-хромозоми /Хр 22.32/. При липса или делеция на едната Х-хромозома се проявяват клиничните белези, характерни за т.нар. Търнеров фенотип - нисък ръст, скелетни аномалии, хипоплазия на шийни прешлени и къса шия, лицеви особености, микрогнатия щитовиден гръден кош, сколиоза, cubitus valgus и др. (25, 31, 32, 49, 50).

Хаплоинсуфициенцията на SHOX - гена най-вероятно

Таблица 1. Хромозомни аберации при синдрома на Turner (по E. Banning 2006)

Генотип	Честота	Симптоматика
45X	50% - 60%	Сърдечни и бъбречни малформации, лимфедем
45X/ 46XX, 45X/ 47XXX /мозайки/	20%	По-висок ръст, спонтанен пубертет в 40%
46Xi (Xq)- изоформи		Автоимунни заболявания
46Xr (X) - ринг форми	Общо 30%	Умствено изоставане
46XXp-, 46XXq- делеция		
45X/46XY, 45X/46XX/47XXY		Вирилизация

има значение за ниския ръст и при други заболявания като идиопатичен нисък ръст и дизостозата на Leri-Weil (31, 41).

При анализ на пациенти с делеция на т.нар. псевдоавтозомен сегмент на Х-хромозомата, освен SHOX-гена е изолиран още един ген, съдържащ транскрипционен фактор, който се експресира в остеобластите (pseudoautosomal homeobox containing osteogenic gene - PHOG). Откритата делеция на този ген при пациенти с нисък ръст го прави възможен кандидат за участие в патогенезата на ниския ръст при синдрома на Turner (13).

Гонадната дисгенезия е също много чест, дори водещ симптом при синдрома, в 80%-100% от случаите. Води до овариална хипофункция, липса на пубертет и инфертилитет. Само при 2% до 5% от мозаичните кариотипи има нормална овариална функция, рядко спонтанен пубертет Локусът на гена, определящ развитието на яйчника се намира на Хр 11.21 - Хр22.1 (49, 50).

Честотата и вида на характерните симптоми са представени на **табл. 2.**

Сърдечно-съдовите аномалии определят намалената продължителност на живота. Описани са коарктация на аортата /30%/, бикуспидална аортна клапа /25%-55%/, аортна дилатация и аневризма /25% - 50%/, дисецираща аорта, аортна руптура (15, 20).

Описани са разнообразни вродени бъбречни малформации като аплазия, подковообразен бъбрек, двойно легенче и двоен уретер От скелетните малформации характерни са нарушени телесни пропорции с по-къси крайници, щитовиден гръден кош, сколиоза, хипоплазия на шийни прешлени, cubitus valgus, къси IV-та и V-та метакарпални и метатарзални кости, деформация тип Madelung в гривнена става, остеопороза. Кожните симптоми включват пигментни неви, дисплазия на ноктите, алопеция, витилиго, келоиди (21).

Съобщава се висока честота на автоимунни заболявания - автоимунен тиреоидит с висок титър на антитиреоидни антитела в 60% от случаите, целиакия, захарен диабет, тиреотоксикоза, псориазис (12).

Напоследък се описват нарушения във въглехидратната и липидна обмяна - нарушен глюкозен толеранс, инсулинова резистентност, дислипидемия, затлъстяване с абдоминален адипозитет, захарен диабет първи и втори тип (7, 14, 48).

Описаните симптоми оформят т.нар. Търнеров фенотип, с характерни психологични проблеми, поради ниския ръст, липсата на пубертет и особеностите във външния вид. Налице е дефицит в социалните контакти, ниска самооценка, понижено самочувствие. Във връзка с това качеството на живот на тези момичета е понижено (35, 36). Умственото развитие обикновено е нормално, с известни затруднения в изучаване на математика и в моториката. Изоставане има само при пациентки с ринг Х-хромозома (44).

ЛЕЧЕНИЕ

Момичетата със синдром на Turner без лечение най-често оставаха инфантилни, без пубертетно развитие и достигаха краен ръст 142 - 144 см., средно с 20 см под ръста на контролната популация (6, 28, 29). Въпреки че при тях не се откриват отклонения в синтезата и секрецията на растежен хормон, се оказа че той може да повиши растежната скорост. Опитът да се ускори растежа с обикновени терапевтични дози на рекомбинантен човешки растежен хормон (rhGH) обаче не доведоха до задоволителен растежен ефект (33). Прилагането по-късно на високи дози от хормона в началото имаха разнопосочни резултати, поради редица причини, като различия при подбора на пациенти, при дозировката на медикамента, във възрастта на пациентките в началото на лечението и в провеждането на допълнителната заместителна терапия с естрогени (9, 11).

Поради овариалната дисгенезия само около 20% от момичетата със синдром на Turner имат спонтанен пубертет (22). При останалите се налага индукция на пубертета с естрогени. Проведените наблюдения са с разнопосочни резултати, което доведе до препоръка за възможно по- късно въвеждане на естрогенна терапия. Това обаче има своите неблагоприятни последици, като остеопороза и възникване на психологични проблеми. (24, 26, 27, 29).

ТЕРАПИЯ С rhGH

Тъй като стандартните терапевтични дози на rhGH не дадоха очаквания растежен ефект, започнаха опити за лечение с високи дози в различни рандомизирани проучвания (42,45)

Rosenfeld и сътр (1986) са едни от първите изследователи на растежния ефект на rhGH при момичета със синдром на Turner. През 1998 г. те провеждат отново едно мултицентрово проучване, при което съобщават краен ръст 150,4 +/- 5,5 см, като при комбиниране на растежния хормон с анаболни стероиди резултатът е по-добър - 152 +/-5,9 см. (33, 34)

Първото мащабно рандомизирано изследване на резултатите от терапията с rhGH е проведено в Канада от Canadian GH- Advisory Committee през 2005 година. Освен това широки наблюдения са провеждани в Белгия, Холандия, Германия, Япония,

Таблица 2. Най-чести клинични сиптоми при синдром на Turner (по E. Banning 2006)

Симптоми	Честота	Локализация на гена
Нисък ръст	80% - 100%	Дефицит или липса на SHOX-ген, Хр22.32
Гонадна дисгенезия	80% - 100%	Липса на ген за развитие на оварии, Хр11.21, Хр22.1
Сърдечно-съдови аномалии	45% - 75%	
Бъбречни аномалии	40% - 59%	
Автоимунни заболявания		Изохромозома Х - с висок риск
ТАТ и МАТ ↑	60%	
целиакия	6,4%	
Скелетни аномалии		Дефицит на SHOX - ген

Израел и др от редица изследователи. Massa. и сътр.. Banke и сътр., Hochberg и сътр, Tanaka и сътр., Bannink и други (2, 17, 22, 28, 29, 42).

Многобройните проучвания на ефекта на rhGH върху растежа проследяват влиянието на различни показатели върху растежния прираст:

= начален ръст и начална костна възраст
= възраст на началото на лечението
= възраст на началото на спонтанния пубертет
= големината на пубертетния растежен скок
= средно-родителския ръст
= дозата на rhGH
= заместителната терапия с естрогени

За оценка на ефекта от лечението с растежен хормон се използва достигнатият краен ръст (FH). По литературни данни той варира от 148,5 см до 152,2 см (17, 19, 24,26, 27).

Около 65% от лекуваните деца достигат FH по-голям от 150 см. (22). В проучванията на Massa (2003) се съобщава краен ръст 151 +/- 6 см, като в сравнение със средно-родителския ръст дефицитът е средно 9,8 +/- 6,4 см , по-добри резултати от тези на Hochberg и сътр., при които растежния дефицит е 16 +/- 4,6 см, По-лош растежен прираст се отчита при по-нисък начален ръст, което потвърждава значението на генетичния потенциал. Най-добри резултати съобщава Bannink (2006) в една мащабна добре проведена терапия на 3 групи пациентки лекувани с малки, средни и големи дози rhGH - най-добрият краен ръст е 163,6 см.- **табл. 3.** Видно е, че има значителна вариабилност в получените резултати, съобщени от различни автори (3, 5). Особено влияние върху крайния ръст има средно-родителският ръст, началната костна възраст и т.нар. catch-up growth през първата година от лечението (22).

Най-добри резултати съобщават автори от Холандия, с краен ръст 163,6 см и растежен прираст от 11,9 см до 16,9 см. (2). **табл.3** -Вариабилността на получените резултати подчертава необходимостта от индивидуализиране на лечението, в зависимост от определящите фактори (38, 43).

Странно е, че в такива мащабни проучвания като това на Massa и сътр. (2003) не се установява зависимост между крайния ръст и някои важни показатели като спонтанния и индуциран пубертет. Децата със спонтанен и индуциран пубертет в това проучване достигат еднакъв краен ръст - 151,3+/-6,3 см при първия и 151,8+/-6 см при втория. Подобни са резултатите и на Reiter и сътр. (22, 27).

За разлика от тях обаче други автори намират, че спонтанният пубертет понижава крайния ръст, в сравнение с индуцирания, въпреки по-големия пубертетен растежен скок при първия - 15,4 +/- 4,6 см срещу 8,6 +/-4,3 см при втория. Вероятната причина за това е, че спонтанният пубертет при момичетата с този синдром настъпва по-рано, между 11 и 13,5 години, в сравнение с индуцирания, който се предизвиква след 13,5 годишна възраст (5, 23, 24).

На **таблица 3** е представен начин на дозиране на растежния хормон от цитираните автори в милиграми или в единици. По този начин може да се сравнят прилаганите дози от различните изследователи. Някои автори са прилагали малки, средни и големи дози (1, 2).

При използването на по-малки дози в някои групи пациентки са добавяни анаболни стероиди (1, 30) **(табл. 3).**

ТЕРАПИЯ С ЕСТРОГЕНИ

Поради овариалната дисгенезия около 80% от момичетата със синдром на Търнер нямат спонтанен пубертет (22). При тях се налага индукция на пубертетното развитие с прилагане на естрогени, класическият ефект на които обаче е ускоряване затварянето на епифизарните фуги и спиране на растежа. Проведените наблюдения от лечението с естрогени са разнопосочни, дори със съобщения за редуциране на крайния ръст. (5, 24, 27). Във връзка с това се предлага:

1. въвеждане на естрогенната терапия възможно най-късно, макар че се развива остеопороза и възникват тежки психологични проблеми (2, 10, 35, 37).
2. да се започва с малки дози 17-beta estradiol, като постепенно се увеличава дозата до достигане на максималната заместваща дозировка. Една добра схема предлага Banning (2006), представена на **табл. 4** (2).

Таблица 3. Дозировка на rhGH (1,2,6, 15, 22, 30, 40)

автор	мг/кг/седм	мг/кг/дн	Е/кг/седм	Е/кг/дн	Краен ръст в см	Заб.
Massa	0,33	0,047	0,98	0,14	151,7+/-6	
Canada	0,30	0,042	0,89		0,12	11
Stephure	0,37	0,053	1,01	0,159		
Bannink						
I gr	0,31	0,045	0,93	0,13	157,6	SDS -1,6
II gr	0,46	0,067	1,38	0,19	162,9	SDS -0,7
III gr	0,63	0,090	1,89	0,27	163,6	SDS -0,6
Anderson-	0,23	0,033	0,69	0,099		+андрогени
	0,46	0,066	1,33	0,19		0,05мг/кг
Gawlik	0,37	0,053	1,01	0,159	148,5	
Ramos	0,17	0,02	0,50	0,07		+андрогени

Таблица 4. Индукция на пубертета при синдром на Turner (по E. Bannink 2006)

Продължителност на лечение с 17-beta estradiol	Доза на 17-beta estradiol	Progesterone - доза и продължителност
Първите 2 години	5 микрогр/кг/дн	не
През 3-тата година	7,5 микрогр/кг/дн	5 мг/дн 14 дни от месеца
От 4-тата година	10 микрогр/кг/дн	5 мг/дн 14 дни от месеца
След спиране на rhGH	1 мг/дн до 2мг/дн	10 мг/дн 14 дни от месеца

Забележка: *Дозировката от 5 микрограма 17-beta estradiol е еквивалентна на 0,05 микрограма ethinyl estradiol*

Лечението с естрогени започва след хронологична и костна възраст 13,5 години и продължава като заместваща хормонална терапия през целия живот по схема, със съответна добавка на прогестерон.

Добавянето на малки дози естрогени към терапията с растежен хормон има добър терапевтичен ефект. Освен индукция на пубертета, те подобряват костната плътност, липидния профил, физическата активност, сърдечно-съдовите смущения и когнитивните функции. Естрогените предизвикват развитието на гръдни жлези и на вътрешните полови органи, но с 2 години по-късно от нормалната популация. Размерите на матката на 20 годишна възраст съответстват на тези на 15 при нормалната популация. Появата на пубертет и нормализиране на ръста подобрява самочувствието и повишава самооценката на пациентките, а с това и социалните контакти и качеството на живот (2, 27, 47).

Началото на естрогенната терапия е свързано не само с хронологичната и костната възраст, но и с лечението с растежен хормон. Предлага се лечението с естрогени да започне най-малко 2 до 4 години след началото на лечението с rhGH, за да има достатъчно време за стимулация на растежа и осигуряване на добър растежен прираст преди настъпването на пубертета. Комбинираната терапия с rhGH + 17-beta estradiol трябва да се провежда така, че естрогените да не пречат на ефекта на растежния хормон. Предимството на рано въведената терапия с растежен хормон е не само по-изразеното ускоряване на растежа с добър catch-up growth през първите 2 години от лечението, поради по-малката костна възраст. Към това се прибавя възможността периодът за самостоятелно лечение с растежен хормон до въвеждане на естрогени да бъде по-дълъг (8, 22, 27, 38, 47).

Според повечето автори рано започналото лечение с растежен хормон може да предотврати или да намали прогресирането на изоставането в растежа и да направи възможно започването на естрогенната терапия по-рано, в по-малка възраст, съответна на пубертетната възраст при контролите. От една страна отлагането въвеждането на естрогени подобрява възможностите за растеж, но от друга своевременното им започване и по-ранното индуциране на пубертета разрешава някои психологични проблеми, подобрява остеопорозата и психосоциалното поведение. Остават известни трудности в моториката и справяне с математиката (2, 8, 24).

За да се уточни дали лечението с растежен хормон влияе върху някои рискови фактори за сърдечно съдови и обменни заболявания някои автори са правели изследвания на глюкозния толеранс, инсулиновата активност, серумните липиди, кръвното налягане и телесните пропорции (48). Резултатите показват, че HbA 1 C остава в референтни граници, базалните и стимулирани инсулинови нива се повишават, IGF-1 достига горната граница на нормата, BMI остава висок, но абдоминалният адипозитет и инсулиновата резистентност намаляват, нормализира се нарушения глюкозен толеранс, кръвната захар е в нормални граници.

Лечението с rhGH се спира при растежна скорост 1-2 см/1 година и костна възраст 18 години. Заместителната хормонална терапия с естрогени продължава цял живот (2, 30, 40).

Странични действия от предписаните високи дози растежен хормон не са описани. Приема се, че лечението на синдрома на Търнер с човешки рекомбинантен растежен хормон е безопасно.

Не се установява миокардна хипертрофия, има запазена бивентрикуларна функция и сърдечна честота, изследвани 6 месеца след спиране на терапията (46).

Ранната терапия обаче често се възпрепятства от това, че диагнозата на синдрома на Търнер се поставя късно, понякога след 12 дори след 15 годишна възраст, особено при мозаечните форми и при микросимптоматика (15, 22, 39). Комбинацията между нисък ръст, гротескно лице, спрегнати аномалии и липса на пубертет насочва към диагнозата. При всяко момиче с нисък ръст е необходимо да се изключи този синдром. Възможна е пренатална диагноза чрез изследване на кариотипа в амниотична течност.

В заключение на известните досега резултати и за да се постигне добър краен ръст, близък до прогнозирания, трябва да се подчертае, че лечението с rhGH при момичета със синдрома на Търнер трябва да започне възможно рано, преди костна възраст 9 години и при ръст под 5-ия перцентил, най-рано на 2 годишна възраст.Терапията с малки дози естрогени да се въведе не по-късно от 15 годишна възраст, при костна възраст 13 години. Необходимо е мултидисциплинарно наблюдение на тези пациенти, поради риск от редица заболявания в по-късна възраст като нарушен глюкозен толеранс, захарен диабет I-ви и II тип, ранна коронарна болест (2, 4).

Въпреки че в първите години на 21 век вече е установено, че лечението на момичета със синдрома на Turner с rhGH подобрява крайния ръст все още остават неизяснени въпроси именно:

- каква е оптималната възраст за начало на терапията с растежен хормон и с естрогени.
- какви са точната дозировка на медикаментите и продължителността на прилагането им
- какво е влиянието на възрастта в началото на лечението и появата на спонтанен пубертет за крайния ръст
- има ли странични явления от високите дози на растежния хормон.

По всички тези въпроси продължават проучванията в реномирани клиники на света.

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GP News
Новини за общопрактикуващия лекар
БРОЙ 4 (131) ГОДИНА 12, АПРИЛ 2011 г. ISSN 1311-4727 ЦЕНА 3.00 ЛВ.

Тема на броя

УРОЛОГИЯ И НЕФРОЛОГИЯ

Тема на броя урология и нефрология

Съдържание

В бр. 3/2011 на списание GP News в статията "Fucidin H и Fucicort – по-добрият избор при лечение на атопичен дерматит и екземи" на ***д-р Даниела Грозева****, докторант в Клиниката по кожни и венерически болести, Университетска болница, Плевен, е допусната грешка в изписването на името на авторката.* ***Екипът на редакцията поднася своите извинения на д-р Грозева.***

2000 места за лекари и зъболекари в чужбина предложи третата международна борса "Кариери в бяло"

Трето издание на международната борса „Кариери в бяло" за лекари, зъболекари, фармацевти, медицински и здравни специалисти се проведе в началото на април в София. Форумът предложи над 2000 работни позиции за всички медицински специалисти, които търсят работа и възможности за реализация и успешна кариера в чужбина. Десет посреднически агенции дадоха възможност на лекарите да избират и да кандидатстват за свободни работни места в болници в Англия, Германия, Франция, Дания, Швеция, Белгия, Испания, Ирландия, като средното възнаграждение на одобрен кандидат е 2500 евро месечно. Организаторите гарантират успешна кариера на всеки български кандидат - дипломиран лекар или студент, в европейските столици и големи градове, като предлагат богати възможности за избор на най-подходящата професионална реализация в областта на медицината и здравеопазването.

Всеки посетител имаше възможност за индивидуална безплатна консултация, за да се ориентира къде и кои са най-атрактивните места за работа, какво е най-оптималното заплащане. Участието и регистрацията във форума „Кариери в бяло" (http://careersinwhite.org) са напълно безплатни.

Третото издание на международната борса се проведе през март - април 2011 г. в шест важни медицински центъра в Румъния, два в България, Унгария и Гърция.

МЗ залага 10% намаляване на смъртността от сърдечносъдови и онкологични заболявания до 2020 г.

Намаляването на смъртността от онкологични и сърдечносъдови заболявания с 10% до 2020 г. е сред основните цели на новия проект на Програма СИНДИ на МЗ. Програмата е насочена към профилактиката на незаразните заболявания и обхваща 9 области в страната с общ брой на покритото население в тях около 700 000 души.

Резултатите от изминалия десетгодишен период на действие на програмата показват, че е нараснал относителният дял на хората, които контролират основните рискови фактори за здравето си. С около 80% се е увеличил броят на българите, които са овладели вредните навици, които водят до високо кръвно, с 30% на хората, които внимават как живеят, за да нямат висок холестерол, а с 50% на тези, които следят да имат нормално тегло. Хората в деветте области, в които действа СИНДИ, са започнали да се хранят по-здравословно, да ядат повече пилешко месо, по-малко сол, да не пият и пушат толкова много.

Намаляване честотата на артериалната хипертония сред младите хора с 15% и повишаване контрола над високото кръвно сред възрастните хипертоници в следващите десет години са сред основните цели на СИНДИ. Също така редуцирането на смъртността от хронична обструктивна белодробна болест с 5% и от пътнотранспортни произшествия с 50%. Сред приоритетите, които си поставят специалистите в програмата, са и намаляването на тютюнопушенето сред възрастните с 10%, а сред бременните жени с 50%. Също така експертите ще се стремят да увеличат с 30% броя на хората, които спортуват.

страняване на конкрементите, намаляването на левкоцитурията, увеличаването на диурезата, нормализацията на pH на урината, процентът на усложненията и тяхното отстраняване.

За критерии за ефективността на Канефрон Н бяха използвани моментът на отстраняване на конкрементите, намаляването на левкоцитурията, увеличаването на диурезата, нормализацията на pH на урината ***(Таблица 3)***.

Изследователска група	Спонтанно премахване на камъните (първите 10 дни)	Екстракорпорална ударно-вълнова литотрипсия	Уретероскопии с екстракция	Вкарване на стент в пикочопровода
Група А n=36	12 (33.3%)	24 (66.7%)	–	–
Група В1 n=24	9 (37.5%)	12 (50.0%)	– –	3 (12.5%)
Група С1 n=15	6 (40.0%)	6 (40.0%)	1 (6.7%)	2 (13.3%)
Група D1 n=27	15 (55.5%)	7 (25.9%)	4 (14.8%)	1 (3.8%)

ТАБЛИЦА 5. *РЕЗУЛТАТИ ПРИ ПАЦИЕНТИТЕ ОТ КОНТРОЛНАТА ГРУПА*

РЕЗУЛТАТИ И РАЗЯСНЕНИЯ

Процентът на спонтанно отстраняване на камъни през първите десет дни на лечението при пациентите от изследователската група, на които беше даван Канефрон Н, беше очевидно по-голям в сравнение с контролната група и пациентите се нуждаеха от по-малко допълнителни мерки за лечение ***(Таблица 4 и 5).***

Липсата на левкоцитурия (след 10-дневно лечение) беше установена при 81 (93.1%) пациенти от първата група и при 21 (46.6%) пациенти в контролната група.

Очевидно е, че прилагането на Канефрон Н в комплексната терапия на бъбречно-пикочната литиаза улеснява спонтанното отстраняване на конкременти независимо от тяхното местоположение. Това се определя от неговото спазмолитично, диуретично, антибактериално и противовъзпалително действие.

ЗАКЛЮЧЕНИЯ

1. Прилагането на Канефрон Н в комплексното лечение на бъбречно-пикочна литиаза улеснява спонтанното отстраняване на малки камъни (0.3-0.6 см) независимо от тяхното местоположение.
2. Препаратът Канефрон Н значително намалява левкоцитурията при пациенти с бъбречно-пикочна литиаза, свързана с инфекция на пикочните пътища.
3. Той повлиява увеличаването на киселинните продукти, включително на пикочната киселина, чрез поддържане нивото на pH на урината в рамките на 6.2-6.8.
4. Лекарството Канефрон Н може да се прилага с цел предотвратяване появата на пикочна литиаза. ❑

Психосоциални проблеми при момичета със синдром на Turner

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Има значителен брой проучвания на психосоциалните проблеми при деца с различни хронични заболявания като астма, муковисцидоза, диабет, хемофилия и други кръвни заболявания, хронични артрити, особено при пациенти с различна степен на инвалидност. Хроничните заболявания влияят върху различни аспекти от живота на болните деца. Например средната самооценка на качеството на живот на деца с муковисцидоза е 3.75, на физическото им състояние - 28.1, на емоционалното им състояние - 23.1, на социалните им взаимоотношения - 19.3, на бита им и полаганите за тях здравни грижи - 24.3 (1).

При всяко от заболяванията може да има различия в зависимост от степента на увреждането, ефективността на терапията, прогнозата на заболяването и социалното вграждане на пациента под формата на училищни контакти, спортни занимания, прекарване на свободното време, връзки с приятели. Ниските резултати при самооценката на качеството на живот са показателни за степента на увреждането и за ефекта от проведеното лечение (1).

Особен интерес представляват заболяванията със симптоми на изоставане в растежа и със забавено или липсващо пубертетно развитие, както е при момичета със синдрома на Turner (2, 3, 6, 7, 12, 13, 14, 15).

Търсят се факторите, които влияят в тези случаи на различните психосоциални параметри, като

ПРАКТИЧЕСКА ПЕДИАТРИЯ

Безплатно издание на БПА, брой 8, 2013 г.

ISSN 1311-0756

Гост редактор: Доц. Нарцис Калева-Ходжева

детската и пубертетно-юношеската възраст.

Метаболитният синдром с всички свои характеристики е сериозно предизвикателство както за диагностика и терапия от страна на лекаря, така и за приемане и справяне с него от страна на пациентката и нейното семейство - особено в детската и пубертетната възраст. Именно за това е необходима преди всичко превенция на заболяването. Това би могло да се постигне с възпитание на нашите деца и пациенти в правилно хранене и начин на живот, изпълнен с физическа активност - игри на открито или спортуване в зала. Всичко това би могло да бъде колкото полезно, толкова и изпълнено с детски смях и забавления.

Забележка. Библиографията е на разположение в редакцията.

Заместително лечение с полови хормони при момичета със синдром на Turner

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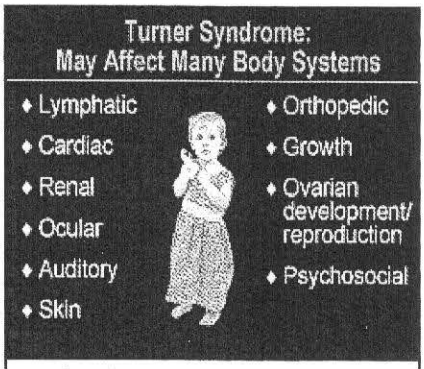
През 1938 г. американският лекар Henry Turner описва детайлно този синдром при 7 пациентки със сексуален инфантилизъм. Немският педиатър Ulrich дава описание на характерната лицева дисморфия през 1930 г., поради което в западната литература този синдром е известен като Ulrich-Turner синдром. През 1962 г. руският лекар Н. А. Шершевски описва синдром при жените, характеризиращ се с нисък ръст, гонадна дисгенезия и асоциирани соматични анормалности. С новите техники на хромозомен анализ Ford и сътр. през 1959 г. откриват, че тези смущения са свързани с 45X кариотип.

Честотата на синдрома е сравнително висока - 1 : 2000 до 1 : 5000 новородени. Реалната честота фактически е по-голяма, но значителна част от зиготите с кариотип 45X загиват.

Двата централни симптома при синдрома на Turner (TS) са изоставането в растежа и хипергонадотропният хипогонадизъм с инфертилитет, дължащ се на гонадна дисгенезия и овариална хипофункция. Към това се описват редица дисморфични белези и малформации - вродени сърдечни пороци, артериална хипертония, вродени бъбречни малформации, скелетни аномалии, характерен лицев дисморфизъм, къса шия и pterygium coli, кожни симптоми. Съобщава се за висока честота на автоимунни заболявания, нарушения във въглехидратната и липидната обмяна и редица психологични проблеми, най-вече дължащи се на основните симптоми (фиг. 1).

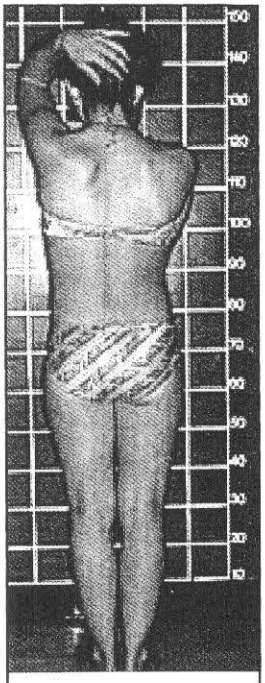


Фиг. 1

Етиологията и патогенезата на синдрома и отчасти необяснимата комбинация от симптоми се изясниха постепенно през последните години. Основната причина е пълна или частична липса на едната Х хромозома във всички клетки на тялото, като в 70-75% от случаите останалата Х хромозома е майчина. Множество гени, разположени на късото рамо на Х хромозомата, са определящи фактори за нормалния растеж, овариалната структура и структурата на други органи. Най-често е комбинацията 45X в 50-60%, при която по-често има сърдечни и бъбречни малформации и лимфедем. Данни за материал на У хромозомата се откриват в 5-10% от пациентките.

Вариабилността на клиничните симптоми се обяснява с различна инактивация на Х хромозомата и отпадане активността на гени, експресирани там - за растежа, за развитието на яйчниците, за познавателната способност и др. Повечето автори смятат, че изоставането в растежа, гонадната дисгенезия и другите аномалии са резултат от отделни генетични дефекти. Според Zinn (1998) е трудно да се идентифицират специфичните гени, отговорни за отделните симптоми, тъй като Х хромозомата кодира голям брой гени.

Ниският ръст при TS е един от генералните симптоми. Среща се в 80-100%. Той се дължи на интраутеринно изоставане в растежа, намалена растежна скорост след раждането и липса на пубертетен растежен скок (фиг. 2). Ниският ръст, скелетните и краниофациалните аномалии се свързват с дефицит или липса на т.нар. SHOX ген (short stature homeobox containing gene on X chromosome). Той е локализиран на терминалния край на двете Х хромозоми (Xp 22.32). Хаплоинсуфициенцията на SHOX гена най-вероятно



Фиг. 2

ПРАКТИЧЕСКА ПЕДИАТРИЯ

Безплатно издание на БПА, брой 11, 2014 г. (година XVI) ISSN 1311-0756

ТЕМА НА БРОЯ: Детска ендокринология

Гост редактор: д-р Елисавета Стефанова, д.м.

Брой 11, 2014
Година XVI

ПРАКТИЧЕСКА ПЕДИАТРИЯ
е специализирано научно списание, предназначено за педиатрите и за общопрактикуващите лекари.

Безплатно издание на Салвис АД съвместно с БПА.

ISSN 1311-0756

Списанието се обработва в БД **Българска медицинска литература.**

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ТЕМА НА БРОЯ

Детска ендокринология - терапевтични насоки

ПОЛЕЗНО ЗА ПРАКТИКАТА

ХРАНЕНЕ

ВАКСИНИ

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КОНКУРС КОНКУРС КОНКУРС

Сп. "Практическа педиатрия" и БПА обявяват конкурс за представяне на клиничен случай на тема **"ПРОБЛЕМИ НА ХРАНЕНЕТО В ДЕТСКА ВЪЗРАСТ"**. С предимство ще се ползват случаите, отразяващи проблеми с наднорменото тегло, затлъстяването, ентералното, парентералното хранене и малнутрицията.

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В конкурса могат да участват всички лекари (педиатри, общопрактикуващи, специализанти и др.) - самостоятелно или в съавторски екип. Участниците имат свобода при избора и формулирането на клиничния случай, който представят, стига да е свързан с темата на конкурса и да представлява диагностичен или лечебен проблем. Статията трябва да е с обем до 4 стандартни страници (4 страници по 1800 знака или максимум 7200 знака общо) и да включва илюстративен материал по избор (снимка/и, фигури, таблици). Представя се и резюме до 500 думи, както и кратка биографична справка за авторите (не повече от 300 думи).

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Приемането на клинични случаи започва от 1 януари 2015 г. и завършва на 30 септември 2015 г. Ежемесечно на страниците на списание "Практическа педиатрия" ще се публикува по един случай, избран от редколегията.

Контакти
Желаещите да се включат в конкурса изпращат материалите на един от следните адреси: konkurs@prakticheska-pediatria.net или spisanie@roditeli.org.
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Лечение с растежен хормон в детска възраст

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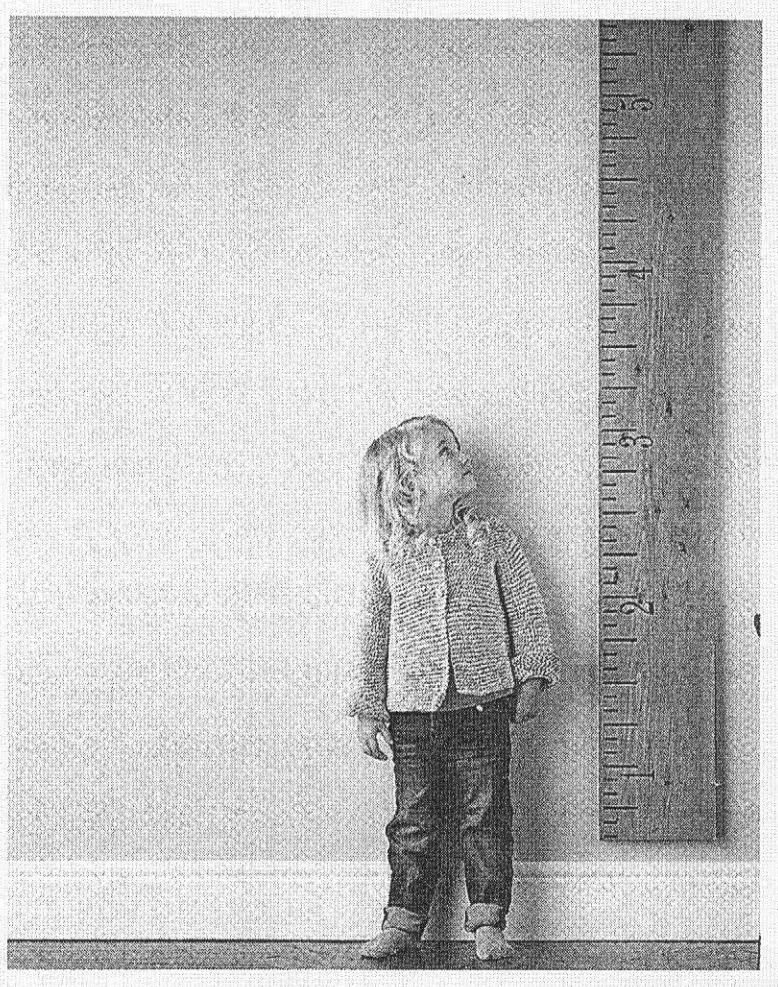

Може би първият човек, който е разпознат като модел на вроден хипопитуитаризъм (дефицит на растежен хормон), е Чарлз Шерууд Стратън (1838-1883), известен като генерал Том Тъмб, който е женен за Лавина Уоран. Снимката на тази двойка ясно показва чертите на нелекуван хипофизарен нанизъм с нормални пропорции между крайници и тяло. В средата на 20-и век ендокринолозите разбират клиниката на дефицита на растежен хормон. Установяват, че растежният хормон (РХ), подобно на инсулина, е протеин. Опитват се да екстрахират РХ от прасета и говеда, но опитите не са успешни. През 1950 г. започва да се използва екстрахиран от човешки хипофизи РХ. През 1960 г. се основават държавни агенции за екстрахиране на РХ от хипофизи, пречистване и дистрибуция до детските ендокринолози за лечение на деца с дефицит на РХ. Такива агенции са създадени в Канада, САЩ, Австралия, Нова Зеландия, Франция, Израел и др. От 1963 г. до 1985 г. в света са лекувани около 27 000 деца с екстрахиран от хипофизи РХ. През 1978 г. лекарите се усъмняват, че болестта на Creutzfeldt-Jacob се предава чрез неврохирургични процедури и трансплантации на корнея. Тя протича с фатална дементна болест на мозъка, известна като спонгиформена енцефалопатия, свързвана с болестта луда крава. През 1970 г. шведската фармакологична компания "Kabi" произвежда първия РХ (екстрахиран от човешки хипофизи) за търговски цели - Crescormon [3, 5].

През 1981 г. американската корпорация "Genentech" в колаборация с "Kabi" започва разработването на рекомбинантен човешки растежен хормон (rhGH), произведен по нова технология (рекомбинантна ДНК), в която човешките гени са вмъкнати в бактерията и може да се произведат нелимитирани количества от този протеин [1, 3, 5].

През 1985 г. избухва скандал с екстрахирания от човешки хипофизи хормон - 4-ма възрастни, получавали от този хормон, се разболяват от болестта на Creutzfeldt-Jacob и той е спрян от употреба, като се замества от новопроизведения рекомбинантен човешки растежен хормон - rhGH. Независимо от високата цена мо-