Alteracions neurosensorials en dones adultes amb Síndrome de Turner

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1.   INTRODUCCIÓ

La síndrome de Turner (ST) és l'anomalia cromosòmica més freqüent en dones, amb una prevalença de fins a 1/2500. Aquesta condició és molt més freqüent intraúter, afectant fins a 1-2% dels embrions, la majoria dels quals acaben en avortaments espontanis (1). La ST està causada per l'absència total o parcial del segon cromosoma sexual en una línia cel·lular com a mínim. Aquest cromosoma pot estar completament absent (monosomia 45,X), o patir diverses alteracions que afecten sobre tot al braç curt (isocromosoma, cromosoma en anell, delecions). La monosomia és la forma més freqüent en limfòcits de sang perifèrica, però l'alteració cromosòmica es pot presentar en forma de mosaic (Figura 1).
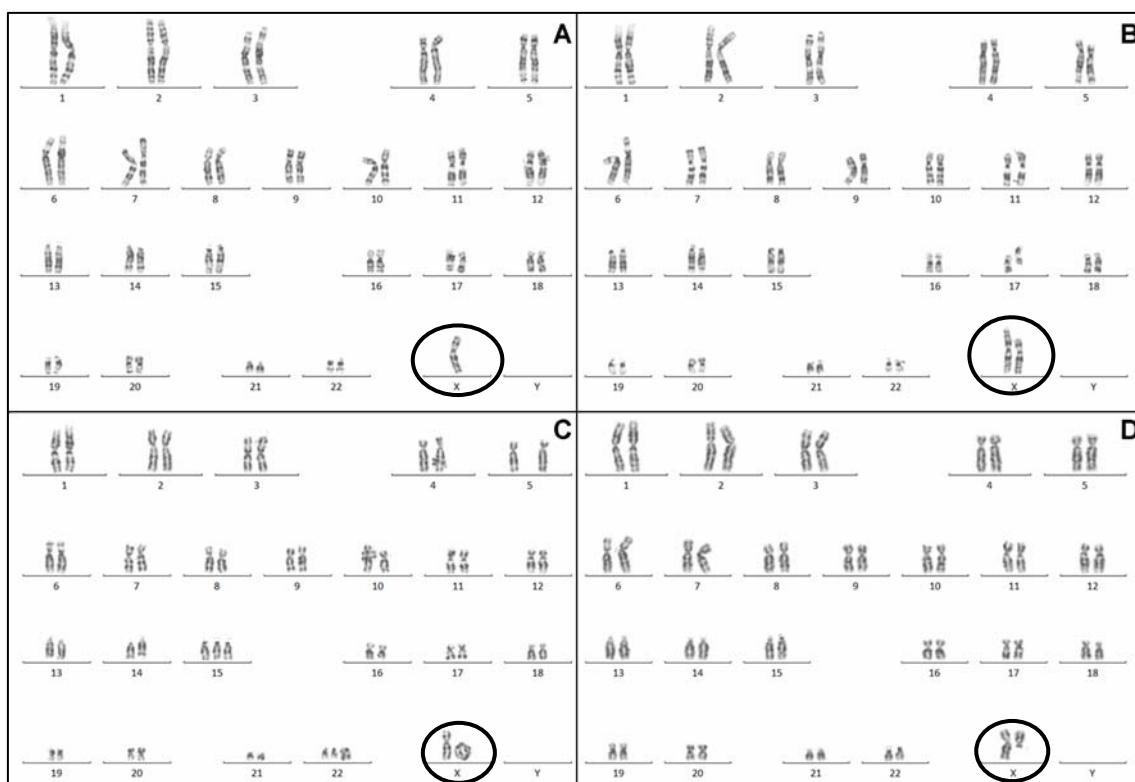
Fig.1 *Exemples de cariotips causants de ST. A) monosomia 45,X. B) isocromosoma del braç curt del cromosoma X. C) cromosoma X en anell. D) deleció parcial del cromosoma X.*

Els signes cardinals de la ST són la insuficiència gonadal i la talla baixa (2). L'hipoestrogenisme causa amenorrea primària i pubertat retardada, i la talla baixa és deguda a una disfunció primària del col·lagen, així com a una insensibilitat parcial a l'hormona de creixement. A més, s'han descrit malformacions cardíaques i renals congènites associades a la ST, i trets característics de dismorfologia. Per aquest motiu, durant anys, la recerca clínica s'ha focalitzat en el diagnòstic precoç d'aquesta síndrome, identificant

alteracions fenotípiques i malformacions congènites, fins i tot en la vida prenatal. Alhora, s'han intentat elaborar protocols d'actuació respecte a l'edat idònia per a iniciar la teràpia hormonal o l'hormona de creixement. Tot això, en l'àmbit pediàtric.

Malgrat això, la ST està vinculada a altres comorbiditats que debuten o s'expressen a l'edat adulta, com les malalties cardiovasculars, diabetis, osteoporosi, malalties autoimmunes organoespecífiques (especialment l' hipotiroïdisme), i alteracions neurosensorials (1,3,4,5). Aquests trastorns augmenten la morbi-mortalitat i redueixen la qualitat de vida d'aquestes pacients. Està justificat, per tant, el seguiment especialitzat i multidisciplinari de les pacients amb ST durant l'edat adulta, que asseguri un cribratge i maneig correcte de les comorbiditats associades. El ginecòleg té un paper fonamental per a indicar i mantenir la teràpia hormonal substitutiva, donar consell reproductiu, i conèixer els protocols de seguiment i derivació a altres serveis.

Citogenètica

La ST es defineix citogenèticament per la monosomia del cromosoma X (45,X), la presència d'un cromosoma X anòmal, o el mosaic combinant 45, X en una línia cel·lular amb un cromosoma X anormal en una altra línia cel·lular (6). La inactivació del cromosoma X, procés anomenat lionització, participa en les primeres etapes de l'embriogènesi en dones amb cariotip normal. En conseqüència, només un cromosoma X és actiu a cada cèl·lula diploide. Aquest procés es produeix normalment d'una manera aleatòria (7), però si hi ha un cromosoma X anormal, aquest serà preferentment l'inactivat (8).

Algunes regions del cromosoma X no són inactivades i, per tant, els gens d'aquestes regions mostren una expressió diploide (9). S'anomenen regions pseudoautosòmiques (PAR) i es troben situades en els extrems del cromosoma (PAR1 en Xpter i PAR2 en Xqter). Es planteja la hipòtesi que el fenotip de la ST es deu a l'haploinsuficiència dels gens situats en aquestes regions. Aquesta afirmació es basa en el fet que 31 d'aquests 34 gens no inactivats es troben en el braç curt del cromosoma X, i la deleció d'aquest braç està altament relacionada amb el fenotip de la ST (10).

Al voltant del 99% dels embarassos que presenten 45,X acaben en un avortament espontani (11). Aquest fet insinua que pot ser necessari un cert grau de mosaïcisme per a la supervivència del fetus (12, 13, 14). La detecció d'aquest mosaïcisme críptic està influenciada per quatre factors: els tipus de teixit analitzats, el nombre de cèl·lules estudiades, la sensibilitat de la tècnica i la proporció de cada línia cel·lular. Així, en aquelles pacients amb baixos percentatges d'aneuploïdia, l'anàlisi estàndard de 15 ó 30 cèl·lules pot no ser suficient per detectar mosaïcismes, i els resultats poden variar en analitzar teixits de diferent estirp.

S'ha establert una certa correlació entre el fenotip i cariotip a la ST, essent la monosomia pura el cariotip més comú i el que es relaciona amb el fenotip més característic (15). Igualment, la presència d'isocromosoma s'ha relacionat amb l'hipotiroïdisme, el cromosoma en anell amb el retard mental, i la talla baixa i la dismorfologia d'extremitats amb l'absència del paquet genètic SHOX situat al braç curt del cromosoma X (2, 4, 16). No obstant, no hi ha una correlació previsible entre genotip i fenotip (2).

Dismorfologia

La talla baixa i la disgenèsia gonadal són els estigmes principals de la ST, acompanyats o no d'altres trets dismorfològics secundaris a l'aparició de limfedema (5, 16). Aquest limfedema és causat per l'absència o hipoplàsia dels vasos limfàtics i s'identifica generalment prenatalment o just després naixement, millorant posteriorment.

La talla baixa és una troballa gairebé invariable en dones amb ST, amb una alçada mitjana final entre 143 i 147 cm a la vida adulta. Es creu que això és degut a un defecte primari de l'os, associat a una insensibilitat parcial a l'hormona del creixement.

SHOX i PHOG són dos gens que han estat identificats com a responsables parcials de la talla baixa, situats a la part distal del braç curt dels cromosomes X i Y (Xp11-22, Yp11). Les mutacions en aquests gens podrien també explicar algunes anomalies esquelètiques associades a la ST, com la deformitat de *Madelung* del canell, el *cubitus valgus* o el quart metacarpià curt.

L'haploinsuficiència d'expressió del gen SHOX podria explicar altres anomalies com ara l'otitis mitjana crònica deguda a la deformitat del conducte auditiu extern, i dificultats per aprendre a succionar, bufar, menjar o articular (2,17).

Degut a la insensibilitat a l'hormona de creixement, les pacients amb ST que van rebre tractament a la infància amb aquesta hormona durant una mitjana de 5,7 anys, van ser de mitjana de 7,2 cm. més altes que el grup control (18). Així, des de l'any 1990, es recomana iniciar el tractament amb hormona de creixement 4 anys abans de la teràpia amb estrògens (1). L'addició d'oxandrolona associada sembla augmentar el guany d'alçada i el desenvolupament del pit sense afectar l'índex de massa corporal (19).

Altres anomalies físiques relacionades amb la ST són l'*epicantus*, les orelles prominents amb deformitat del pavelló auricular, la micrognàtia, el paladar fes, el coll curt, el *pterigium colli*, les extremitats curtes, les orelles d'implantació baixa, i el *cubitus* i *genu* valgum (4) (Figura 2).
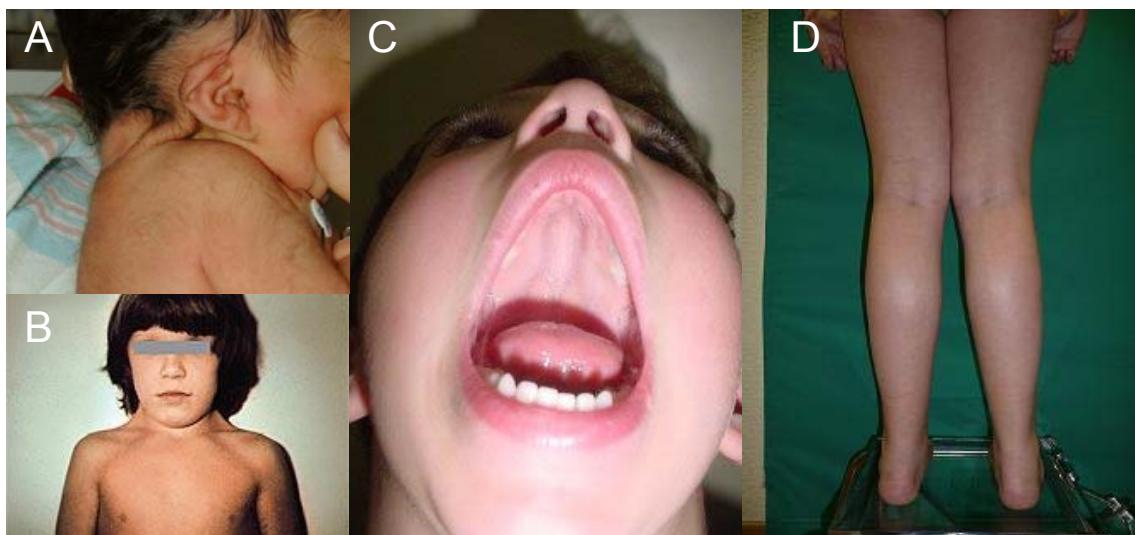
Fig. 2 *Trets dismorfològics característics de la ST. A) limfedema nucal. B) pterigium colli (coll alat). C) paladar ogival. D) genu valgum.*

Disgenèsia gonadal

Malgrat que la diferenciació de les gònades en dones amb ST és normal fins al tercer mes de gestació, es produeix una degeneració accelerada dels oòcits després d'aquest període, amb un augment de la fibrosi de l'estroma ovàric. Conseqüentment, la insuficiència ovàrica es manifesta normalment durant els

primers mesos o anys de vida. L'amenorrea primària és molt freqüent en dones amb ST, però la incidència de menarquia i pubertat espontània és d'un 8% en pacients amb monosomia pura, i s'apropa al 40% en dones amb mosaïcismes (16). Les concentracions d'hormona fol·licle estimulant (FSH) i luteïnitzant (LH) són altes als 5 dies d'edat en nenes amb ST. Tot i què aquests nivells disminueixen posteriorment, es mantenen superiors als nivells de nenes amb cariotip normal (5, 20).

El cromosoma Y està present en el cariotip de fins el 6% de les pacients amb ST. La línia Y en dones pot conduir al desenvolupament d'un gonadoblastoma, una neoplàssia maligna de cèl·lules estromals i germinals. Per tant, es recomana l'extirpació profilàctica de les gònades en dones amb presència del cromosoma Y al seu cariotip, tenint en compte que el risc de gonadoblastoma augmenta amb l'edat (del 2% als 10 anys, al 27,5% als 30 anys) (16). S'acostuma a realitzar la gonadectomia després del desenvolupament puberal, en cas d'ésser aquest espontani.

Teràpia hormonal substitutiva

Després de la inducció de la pubertat amb estrògens, la majoria de les dones amb ST requereixen teràpia estrogènica a llarg termini per evitar els efectes de l'hipoestrogenisme (16, 21). La deficiència d'estrògens provoca pèrdua òssia, disfunció endotelial, disminució de la producció d'insulina, un patró lípidic anormal, augment de l'adipositat central i aterosclerosi precoç. Per tant, l'hipoestrogenisme és un factor de risc cardiovascular. En les dones amb ST i deficiència estrogènica, la teràpia amb aquesta hormona millora l'augment d'enzims hepàtics i alguns dèficits cognitius, com el temps de reacció, la velocitat de processament no verbal, o la memòria a curt termini (22). Per tant, cal mantenir l'ús d'estrògens a dosis fisiològiques fins a l'edat esperada de la menopausa. Tanmateix, és important destacar que ni el risc de càncer de mama ni de càncer d'ovari o endometri és superior en aquestes pacients que en la població general, tot i rebre teràpia estrogènica (5).

Es recomana l'ús d'estrògens naturals d'administració per via oral o mitjançant pegats transdèrmics, tenint en compte la preferència de la pacient o per evitar el metabolisme de primer pas hepàtic. L'etinil-estradiol que contenen les

píndoles anticonceptives s'ha associat amb efectes adversos sobre els enzims hepàtics, metabolisme lipídic i la pressió arterial, tant en dones amb cariotip normal con en dones amb ST. A més, algunes dones amb ST presenten símptomes climatèrics durant la setmana lliure de píndola causats per la completa manca d'estrògens.

El progestagen s'ha d'administrar durant un mínim de deu dies al mes per tal de prevenir el carcinoma endometrial, tot i que un règim continu permet evitar el sagnat menstrual.

Fertilitat i gestació

Respecte a les opcions per a la fertilitat, els embarassos espontanis ocorren en menys del 5% de les pacients amb ST, amb el risc de desenvolupament de malformacions congènites i cromosomopaties en el fetus. Per tant, la fecundació in vitro amb donació d'oòcits és la tècnica recomanada per les pacients amb ST.

Cal tenir en compte que el risc d'avortament espontani durant el primer trimestre és superior al de la població general, malgrat la donació d'ovòcits. Això és probablement degut a una hipoplàsia uterina, amb alteració de les artèries uterines que provoquen isquèmia durant l'embaràs. La taxa d'implantació d'embrions també sembla ser inferior (23, 24).

Els parts solen ser mitjançant cesària, a causa de la desproporció cefalopelviana resultant de l'*habitus* de les pacients amb ST.

La ST està associada a diversos trastorns cardiovasculars, que calen ser avaluats mitjançant ecocardiografia prèviament a l'aplicació de tècniques de reproducció assistida. S'ha descrit recentment un risc de mortalitat per dissecció o ruptura aòrtica durant l'embaràs de fins al 2% en dones amb ST, que persisteix durant el període del postpart a causa dels canvis aòrtics relacionats amb la gestació. Això ha fet concloure al Comitè de la Societat Americana de Medicina Reproductiva, que la ST és una contraindicació relativa per a l'embaràs, però una contraindicació absoluta en una pacient amb una anomalia cardíaca documentada (25). A més, les dones gestants amb ST cal

seguir-les a unitats d'alt risc obstètric, amb controls estrictes de la pressió arterial i el metabolisme hidrocarbonat.

Finalment, el diagnòstic prenatal de la ST permet la predicció de la insuficiència gonadal abans de la fibrosi ovàrica, de manera que les noves tècniques de criopreservació de teixit ovàric, per tal d'oferir un reimplantament posterior, podrien considerar-se en dones seleccionades amb ST.

Osteoporosi

L'osteoporosi associada a la ST sembla ser causada per l'hipoestrogenisme, a més d'un defecte primari en la formació de l'os. Aquest defecte molecular roman sense identificar, però alguns gens situats en el cromosoma X semblen associats amb canvis en el teixit connectiu (26).

S'ha descrit una reducció d'un 25% en el pic de massa òssia en les dones amb ST. Cal tenir en compte, però, que les mesures de densitat òssia depenen de l'alçada, i la talla baixa i el tractament amb hormona de creixement podrien ser factors de confusió que alteren la densitometria òssia d'aquestes pacients. No obstant, la incidència de fractures en les nenes i dones adultes amb ST és 3 vegades superior a la dels controls amb cariotip normal (27).

El tractament amb hormona de creixement durant un any com a mínim, juntament amb la teràpia estrogènica iniciada abans dels 12 anys, sembla millorar la densitat mineral òssia. De fet, les nenes amb ST i menarquia espontània aconsegueixen un pic de massa òssia normal (28).

Alteracions cardíaques

Les complicacions cardiovasculars són la causa principal de l'augment de mortalitat descrita a la ST, amb una reducció de l'esperança de vida de fins a 13 anys. La dilatació de l'arrel aòrtica, la hipertensió arterial i la vàlvula aòrtica bicúspide s'han reportat com les 3 principals complicacions cardiovasculars associades a la ST (29). A més, la mortalitat per malaltia isquèmica coronària s'incrementa fins a 7 vegades en dones amb ST, tot i que els mecanismes

responsables d'aquest augment del risc cardiovascular es no es troben definits amb exactitud (29).

L'hipogonadisme i la conseqüent disminució d'estrògens és una de les causes de l'augment del risc cardiovascular (30), però s'han identificat diferències en l'expressió gènica del cromosoma X que també poden contribuir a aquestes complicacions. S'han descrit diversos gens implicats en el control de la funció cardiovascular en aquest cromosoma, com el gen del receptor d'angiotensina 2 i diverses quinases i factors de transcripció (31).

La valva aòrtica bicúspide és la malformació congènita més freqüent (16%) associada a la ST (Figura 3). Normalment es tracta d'una alteració aïllada, tot i què de vegades s'associa a altres anomalies cardíaques, com la coartació d'aorta. Aquesta combinació pot causar una disfunció valvular progressiva degut a la calcificació de la valva aòrtica, provocant estenosi aòrtica o regurgitació durant l'edat adulta. La coartació d'aorta afecta el 10% de les dones amb ST. A més de ser una de les causes d'hipertensió arterial, sembla estar associada amb la presència de limfedema sever, possiblement per causa del flux limfàtic anormal degut a la compressió de l'aorta ascendent (2, 32).

Fig. 3 *Valva aòrtica bicúspide.*

Altres anomalies cardíaques associades a la ST són el drenatge venós anòmal parcial i el prolapse de la vàlvula mitral. Les anomalies del costat esquerre del cor s'associen a l'endocarditis, i cal recordar que els antibiòtics profilàctics són essencials abans de procediments quirúrgics.

Malgrat això, el risc cardiovascular més sever en dones amb ST és la dissecció aòrtica, que pot ocórrer a qualsevol edat, causant fins i tot la mort sobtada. Per tant, cal incloure l'ecocardiografia en l'avaluació de pacients amb ST i s'hauria d'indicar periòdicament, doncs pot debutar durant l'edat adulta en un cor prèviament sa.

Igualment, cal realitzar un electrocardiograma en el seguiment de les dones amb ST, doncs s'han reportat defectes de conducció o de repolarització atribuïts a la disfunció neuroautonòmica de les pacients amb ST (2).

En resum, la hipertensió arterial, una valva aòrtica bicúspide i l'arrel aòrtica dilatada són factors de risc de dissecció aòrtica. Per tant, és esencial el control estricte de la tensió arterial en dones amb dos d'aquests tres trastorns (33).

Alteracions metabòliques

Les pacients amb ST tenen una major prevalença d'altres factors de risc cardiovascular, com la dislipidèmia i la diabetis *mellitus* per resistència a la insulina (16). La diabetis *mellitus* tipus II és de 2 a 4 vegades més comú en dones amb ST, i s'ha descrit un defecte metabòlic precoç que afecta la captació de glucosa. La resistència a la insulina i la hiperinsulinèmia secundària no semblen dependre de l'índex de massa corporal, tal i com s'ha descrit a la síndrome d'ovari poliquístic. Tot i això, l'obesitat central descrita en dones amb ST pot empitjorar aquest defecte. A més, la hipertrigliceridèmia pot ser una conseqüència de la hiperinsulinèmia i l'obesitat.

La hipercolesterolèmia es produeix a costa d'un augment de les lipoproteïnes de baixa densitat, seguit per una disminució de les lipoproteïnes d'alta densitat. La teràpia amb hormona de creixement pot agreujar aquest trastorn, però l'efecte és reversible en interrompre el tractament (34).

Els enzims hepàtics es troben discretament elevats en les dones amb ST, però sembla una disfunció transitòria i benigna. No obstant això, aquestes pacients tenen un risc de cirrosi augmentat fins a 5 vegades (1). Per tant, la funció hepàtica s'ha de revisar periòdicament.

En conclusió, un estret control de la pressió arterial, així com una determinació anual del perfil de lipídic, de carbohidrats i de la funció hepàtica han de formar part del protocol de seguiment de les dones amb ST durant l'edat adulta.

Malformacions renals

Les malformacions renals congènites són fins a 9 vegades més freqüents en dones amb ST que en la població general (16). Aquestes anomalies inclouen el ronyó en ferradura, el doble sistema caliciliar, l'agenèsia renal unilateral o malrotacions renals (Figura 4). Les malformacions renals són més comunes en les dones amb monosomia pura, i no es troben relacionades amb la hipertensió arterial ni amb altres símptomes clínics. No obstant això, es recomana la realització d'una ecografia renal en el moment del diagnòstic (normalment durant l'edat pediàtrica), que cal repetir en el traspàs cap a la vida adulta.

Alteracions immunològiques

L' hipotiroïdisme afecta fins al 70% de les pacients amb ST, especialment de causes autoimmunes. També s'han observat elevacions lleus i transitòries de la TSH, sense la presència d'autoanticossos tiroïdals. Per tant, cal revisar anualment la funció tiroïdal per tal de diagnosticar precoçment el desenvolupament de l' hipotiroïdisme.

De fet, els autoanticossos i conseqüentment, les malalties autoimmunes, tenen una prevalença incrementada en les dones amb la ST. Destaquen la malaltia celíaca, la malaltia inflamatòria intestinal (colitis ulcerosa i malaltia de Crohn), el vitiligen i l'alopècia *areata,* la insuficiència suprarenal, l'artritis idiopàtica juvenil i la diabetis *mellitus* tipus I (35, 36, 37). El gen FOXP3, situat a una regió del cromosoma X, pot estar relacionat amb aquests trastorns autoimmunitaris. El gen FOXP3 defineix la síndrome IPEX, una síndrome que associa diverses malalties autoimmunitàries. L'expressió del FOXP3 es correlaciona amb la dels leucòcits CD127low (leucòcits amb baixa expressió CD127) (38), i s'ha suggerit que aquesta alteració pot justificar un augment en la prevalença de l'autoimmunitat a la ST, especialment entre els cariotips que inclouen isocromosoma del braç curt del cromosoma X (38).
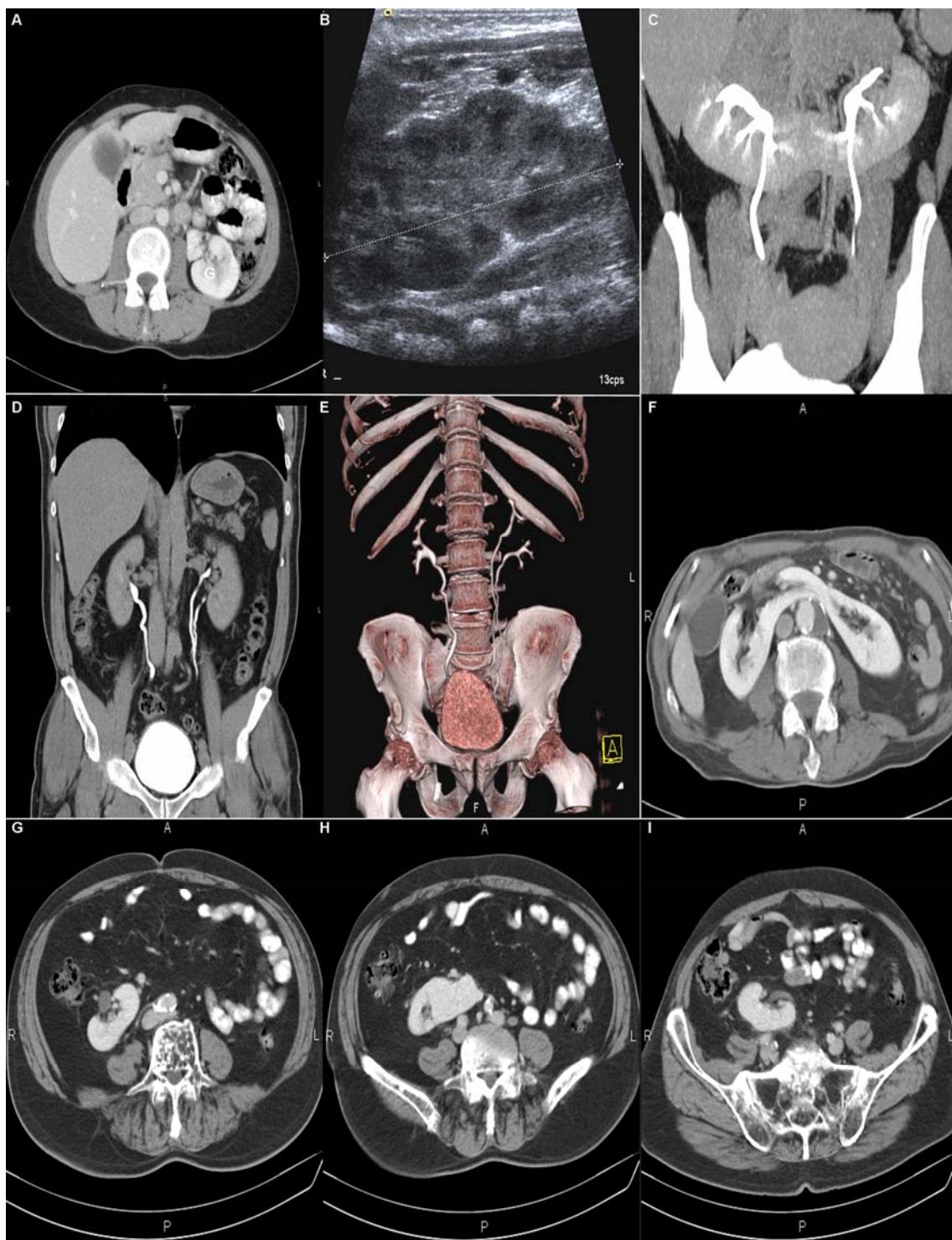
Fig. 4 *Principals malformacions renals congènites associades a la ST. A) Pla axial d'una TAC abdominal mostrant una agenèsia renal dreta. B) Ecografia abdominal mostrant una hipertròfia renal compensatòria contralateral en una pacient amb agenèsia renal. C) Uro-TAC mostrant un ronyó en ferradura. D) i E) Uro-TAC mostrant un doble sistema del ronyó esquerre. F) Pla axial d'una TAC mostrant ronyó en ferradura. G), H), I) Tres plans axials d'una TAC mostrant una malposició del ronyó esquerre.*

També s'han descrit altres trastorns del sistema immune presents en pacients amb ST, per exemple, la disminució en la proporció de limfòcits CD4/CD8, o la baixa concentració d'immunoglobulines. Malgrat aquestes alteracions, no s'han descrit un augment d'infeccions, amb l'excepció de l'otitis mitjana (38, 39).

Alteracions neurosensorials

Pèrdua auditiva

Trastorns neurosensorials com les alteracions olfactòries o la pèrdua d'audició s'han reportat en algunes pacients amb ST (40, 41, 42, 43, 44). Un alt percentatge de dones joves i de mitjana edat amb ST pateixen hipoacússia progressiva, amb un ràpid deteriorament amb l'edat. La pèrdua d'audició de tipus conductiu sembla ser una conseqüència d'episodis repetits d'otitis mitjana durant l'infància. La causa de la infecció està relacionada amb la deformitat del pavelló auricular, que és més pronunciada en pacients amb una deleció total del braç curt del cromosoma X, com la monosomia 45,X o l'isocromosoma (45). Igualment, han estat definits dos patrons de disminució auditiva neurosensorial en pacients amb ST: una caiguda de freqüència mitjana; i una pèrdua d'alta freqüència que sembla relacionada amb l'edat (similar a la presbiacúsia) (41, 44, 45). Per tant, la pèrdua conductiva pot tenir un origen genètic, mentre que la fisiopatologia de les lesions neurosensorials no està encara completament resolta a la literatura. Alguns estudis indiquen que la disfunció coclear és la causa de la deficiència neurosensorial, i la deficiència d'estrògens pot jugar-hi un paper (44, 46).

La relació entre la malaltia otològica i el cariotip (45, 47), l'impacte del tractament amb hormona de creixement i la deficiència d'estrògens sobre l'audició (46, 48, 49), la fisiopatologia de la pèrdua auditiva neurosensorial, o la identificació de marcadors otorinolaringològics per al diagnòstic precoç de la ST (50), són qüestions pendents de resolució.

Alteracions olfactòries i gustatives

Els trastorns en la funció olfactòria són comuns en la població general, sovint associats amb sinusitis cròniques i poliposi nasal, lesions traumàtiques

cerebrals, infeccions del tracte respiratori superior o rinitis al·lèrgica (51, 52). No obstant, més de 200 condicions s'han relacionat amb canvis en l'olfacte, com els trastorns neurodegeneratius, agents químics tòxics o malalties congènites. Com la síndrome de Kallmann, la ST ha estat relacionada amb disfuncions olfactòries i gustatives (53). Malauradament, aquesta associació es basa en observacions anecdòtiques, i els mecanismes responsables de la pèrdua de l'olfacte són poc coneguts. Només han estat publicats dos estudis relacionant l'olfacte i la ST. Es van trobar llindars elevats de detecció i reconeixement de 3 olors en dones amb hipogonadismes a l'any 1967, així com llindars elevats d'agres i amargs utilitzant una prova de gust (54). Valkov va publicar resultats similars en 20 pacients amb ST vuit anys més tard (55). No existeixen altres publicacions a respecte.

Perfil psicosocial

Encara que el coeficient intel·lectual i les habilitats verbals solen ser normals, alguns subjectes amb ST mostren un deteriorament en el processament espai-numèric o discapacitats que afecten el reconeixement o les funcions executives (56, 57). Els pares d'aquestes pacients expliquen una pitjor capacitat de concentració, amb una reducció de la memòria a curt termini. Un cop més, la gravetat del deteriorament cognitiu sembla estar relacionada amb el cariotip, sent pitjor en monosomia pura que en patrons de mosaïcisme (33). També s'han descrit diferències en l'estructura cerebral, com uns lòbuls parietals més petits, o un menor volum prefrontal, que sembla que es correlacionen amb les diferències en les funcions cerebrals (58).

D'altra banda, les pacients amb ST mostren uns trets de personalitat peculiars, amb un grau de timidesa augmentat, més angoixa social i baixa autoestima (59). Aquest perfil condueix a un debilitament de les relacions socials i pitjor rendiment escolar (60). Tot i què la dificultat en la comunicació no verbal pot tenir algun paper, la imatge corporal resultant de la talla baixa, la dismorfologia i la maduració sexual tardana poden influir-hi. Malgrat aquest perfil psicosocial, alguns estudis reporten que les dones joves amb ST presenten una qualitat de vida normal un cop establerta la pubertat induïda (61, 62). La funció sexual sí

sembla alterada en aquestes pacients (63, 64), però la literatura a respecte és controvertida. .

Dificultats psicosocials similars s'han descrit en dones altres causes d'hipogonadismes congènits i cariotip normal, sense dismorfologia física o disfuncions neurocognitives (65, 66). Per tant, si aquestes dificultats són causades pels efectes de la supressió d'un cromosoma X o per la insuficiència ovàrica precoç segueix sent una qüestió pendent de resoldre.

Les dones amb ST haurien de tenir accés als psicòlegs clínics per al tractament de l'angoixa social i per treballar àrees específiques de deficiència. Les famílies haurien de comptar amb el suport per a obtenir una teràpia adequada, incloent adaptacions especials a l'escola (2).

2.   HIPÒTESI DE TREBALL I OBJECTIUS

Hipòtesi

Les dones amb síndrome de Turner (ST) presenten una alta prevalença d'alteracions neurosensorials i altres comorbiditats que afecten la qualitat de vida, sobre tot en les pacients amb cariotips més anòmals.

Objectius

Comprovar si existeix relació entre l'alteració cariotípica i diferents comorbiditats associades a la ST.

Analitzar el cariotip en dos teixits de diferent estirp i augmentar en nombre de metafases analitzades, i avaluar les diferències amb la tècnica estàndard.

Descriure els diferents patrons d'hipoacúsia associats a la ST, amb proves subjectives i objectives. Afegir dades a la literatura sobre la fisiopatologia dels mateixos, tot mostrant el paper de l'hipoestrogenisme congènit.

Esbrinar si existeixen alteracions olfactòries i gustatives en la població amb ST. Si es confirma, analitzar el tipus i la prevalença de les mateixes, i el possible paper de les hormones sexuals.

Valorar l'efecte de la ST i d'altres hipogonadismes congènits sobre la qualitat de vida i la funció sexual.

3.   PUBLICACIONS

1. MANAGEMENT OF TURNER'S SYNDROME IN ADULT LIFE: CASE-SERIES AND SYSTEMATIC REVIEW.

Article publicat a *Gynecological Endocrinology*.

Management of Turner's syndrome in adult life: case-series and systematic review.

Ros C, Castelo-Branco C.

Gynecological Endocrinology és la revista oficial de la Societat Internacional de Ginecologia Endocrinològica. Cobreix tots els aspectes experimentals, clínics i terapèutics d'aquesta disciplina. Inclou documents relacionats amb el control i la funció de les glàndules endocrines en les dones, els efectes dels esdeveniments reproductius en el sistema endocrí, i les conseqüències dels trastorns endocrins sobre la reproducció.

Impact Factor (IF): 1.581; mitjana de l'IF dels últims 5 anys: 1.574. Es troba a l'inici del tercer quartil de l'especialitat d'Obstetrícia i Ginecologia (posició 43/79), d'acord amb el Journal Citation Reports 2011®.

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REVIEW ARTICLE

Management of Turner's syndrome in adult life: case-series and systematic review

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Objective: **To assess the symptoms and outcomes of clinical management in adult patients with Turner's Syndrome.** *Design:* **Retrospective case-series and systematic review of the litera-ture.** *Setting:* **Gynaecological Endocrinology Unit in a teaching hospital.** *Patients:* **Patients followed in the Gynaecological Endocrinology Unit.** *Interventions:* **Review of medical records and a computer search via several databases to identify jour-nals relevant to the subject were performed.** *Main outcome measures:* **Final height, weight, previous treatments with growth hormone, cardiac or renal malformations, metabolic profile, and additional treatment for osteoporosis.** *Results:* **Thirty-one patients were analysed. Differences in final height were found between groups with monosomy and other karyo-types. Four patients bore congenital cardiac malformations, and six, renal congenital malformations. Nine patients had a previous diagnosis of hypercholesterolemia. The most abnormal hepatic parameter was GGT, with fifteen patients having values over the normality limit. Ten patients were receiving treatment for osteopenia or osteoporosis.** *Conclusions:* **This case-series provides recommendations for the management of adult patients with Turner's syndrome and insight into the different medical complaints of this syndrome. A link between karyotypes and clinical features suggests a novel hypothesis to explain the different phenotypes and clinical abnormalities of these patients.**

Keywords: Congenital malformations, gonadal dysgenesia, metabolic abnormalities, osteoporosis, primary amenorrhoea, Turner's syndrome

Introduction

Turner's syndrome (TS) is the most common chromosomal abnormality in females, and affects one in 2500 live female births. This condition is more common *in utero*, affecting 1–2% of all conspectuses. Only 1% of fetuses do not end up in miscarriage [1]. TS is the result of the absence or the abnormality of the second sexual chromosome, in at least one cellular line. The chromosome might be completely lost (45X0), may have undergone duplication of the long arm with the loss of the short one (isochromosome Xq), may transform into a ring formation (rX), or suffer a dele-tion that includes the tip of the short arm. Monosomy 45X0 is the most frequent form in peripheral blood lymphocytes (40–60%), but other karyotypes present mosaic patterns like 45X0/46XX, 45X/46XY or 45X/46Xq-.

TS is associated with a wide array of potential abnormalities, most thought to be caused by haploinsufficiency of genes that are normally expressed by both X-chromosomes [2]. The cardinal features of TS are short stature and ovarian failure with insuffi-cient sex steroids. These dysfunctions cause delayed puberty and primary amenorrhoea in most cases. Most medical attention has therefore been focused on early diagnosis, looking for signs for prenatal diagnosis, or performing paediatric guidelines for treat-ment with growth hormone (GH) and pubertal management [3].

Nowadays, it has become evident that patients with TS are susceptible to some disorders whose beginning or evolu-tion occurs in adult life, such as osteoporosis, hypothyroidism, diabetes, dyslipemia or non congenital cardiac or nepho-uro-logical changes. Morbidity and mortality are increased, and life expectancy is reduced mainly by cardiovascular diseases [1,3–7].

Special care during adulthood is necessary, with coordination among different specialties, in order to develop guidelines for the correct control of sensorineural and endocrine disorders, to seek associated malformations, and for reproductive counselling or sexual health. Gynaecologists should take primary responsibility for the management of these patients to maintain and control hormone replacement, referring them to other specialties if required. In this case-series and systematic review, we describe the complications of patients with Turner's syndrome in adult life.

Material and methods

Retrospective case-series

Thirty-one patients were followed in Gynaecological Endocrinology Unit of the Hospital Clínic of Barcelona. Blood karyotype was performed for TS diagnosis. Weight and height, as well as blood pressure, were controlled on every visit. Metabolic profile was assessed every year. In addition, an abdominal ultrasound, bone absorptiometry and echocardiography were performed on a regular basis during adulthood. Finally, hearing was monitored by audiometry.

Systematic review

A systematic review of studies involving Turner's syndrome was carried out. To identify all of the articles assessing TS in adult ages, the following search strategy was designed: "Turner's syndrome" ([All Fields] and [MeSH Terms]) or "gonadal dysgenesis" ([All Fields] and [MeSH Terms]) or "chromosome aberrations" ([All Fields] and [MeSH Terms]

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or "abnormal karyotype"[All Fields] and [MeSH Terms]) and ("humans"[MeSH Terms] and ("women"[MeSH Terms] or "female"[MeSH Terms]) and "adult"[MeSH Terms]). This strategy was adapted and applied to different Internet search engines to the MEDLINE database (1966-June 2011). There was no language, type of article or date restriction. This search was further supplemented by a hand-search of reference lists of selected review papers. 645 articles were screened, 384 of them assessed for eligibility, and finally 33 were included in qualitative synthesis.

One reviewer (CCB) independently evaluated the eligibility of the trials. One reviewer (CR) extracted the data from the selected articles using a prefixed protocol (information was gathered on the characteristics of the participants in the trial, the intervention and how the results were measured).

When extracting data from the selected reports, those that may be relevant for the management of Turner's syndrome in adult life were picked in a first screening. Afterwards, the most relevant were introduced in the present review. CR undertook

the selection of the data and CCB checked any possible mistake occurred during the first extraction of data.

Of the articles reviewed, those that were not related to this specific syndrome, literature reviews or those whose purpose was not to demonstrate a therapeutic impact or management of Turner's syndrome in adult life were not considered. In the final selection of articles only those using diagnostic techniques, treatments or medical procedures that are currently recognized were taken into account (Figure 1).

Results

Clinical features

Short stature and gonadal dysgenesis are the main clinical stigmata, accompanied or not by other dysmorphology secondary to lymphoedema [5,6]. An association between karyotype and phenotype exists, but it is not predictable. For instance, external dysmorphology and nephrologic or cardiac malformations are common in pure monosomy [1,8], while 40% of patients with

Flow Diagram
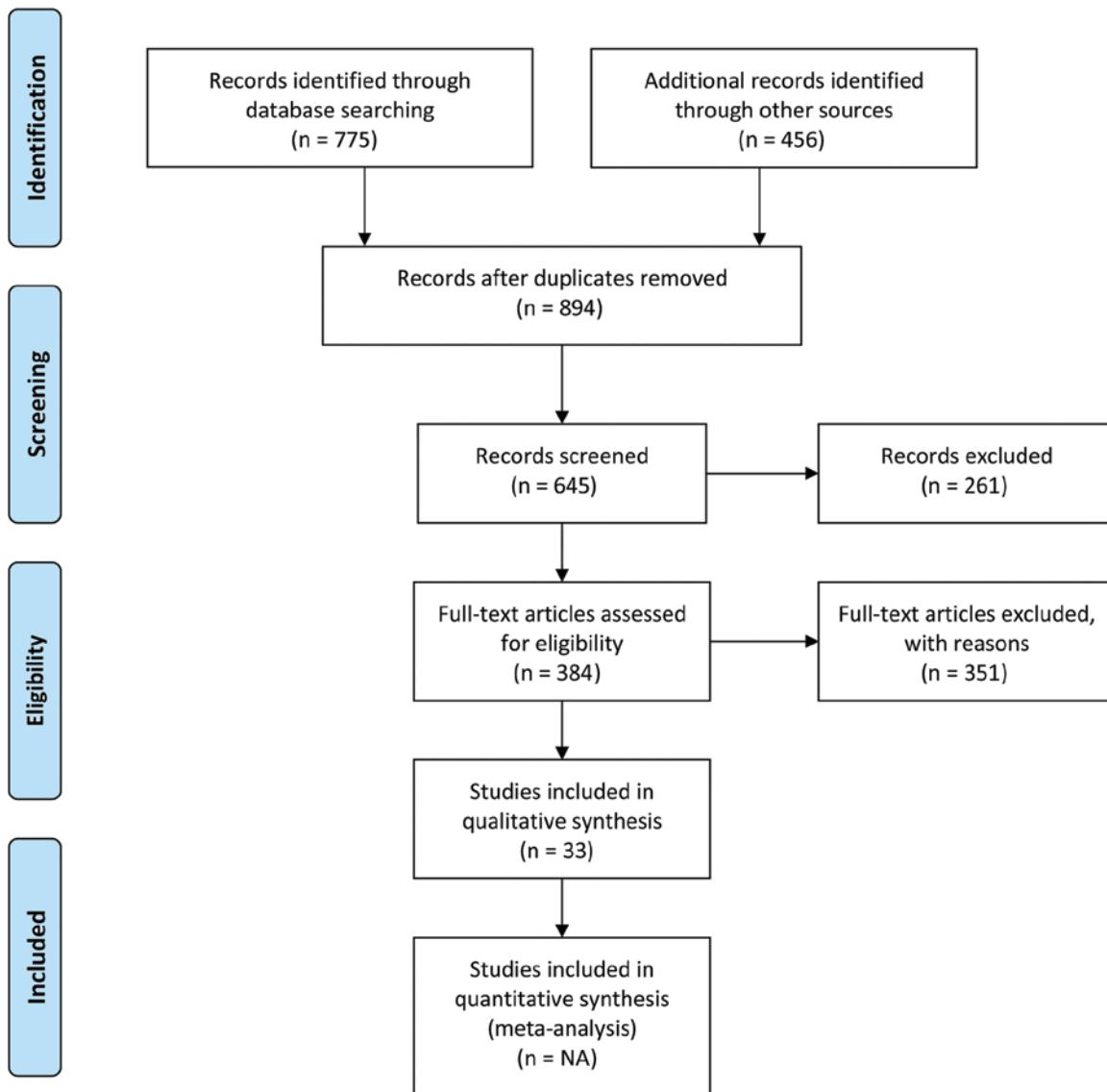
Figure 1. Flow diagram of the studies finally included in the review.

mosaic patterns present spontaneous menarche with fewer external features. In addition, isochromosome is associated with sensorineural and immunological disorders, without congenital malformations.

Short stature is almost an invariable finding in women with TS, with a mean final adult height between 143 and 147 cm. The cause is thought to be due to a primary bone defect, associated with a partial GH insensitivity. Therefore, patients receiving treatment during childhood with GH therapy for a mean of 5.7 years, were on average 7.2 cm. taller than the control group [9]. It is recommended to begin GH treatment 4 years before oestrogen replacement [1], and the addition of oxandrolone associated with GH seems to increase height gain and slow breast development without affecting the body mass index [10].

The peripheral blood karyotypes of all the subjects included in the present case-series are shown in Table I. Table II gives data of the anthropometric measures sorted by karyotype and GH treatment during childhood. As expected, statistically significant differences in final height were found between pure monosomy patients and other karyotypes ($p < 0.05$). However, in our case-series, no differences were found between GH-treated and non GH-treated women, either taking all patients together (147.2 ± 5.7 *vs.* 150.1 ± 8.7, respectively) or divided to karyotypes (Table II). Nevertheless, in this case-series the evaluation of the effectiveness of GH treatment was not possible because the initial height of the TS women was not available, thereby not allowing comparison between initial and final height. In addition, our case-series includes patients from 20 to 50 years old. In the past, TS diagnosis was more difficult than today, and children with major syndromic stigmata (and consequently, shorter) were diagnosed earlier and more easily, receiving GH treatment during infancy. For instance,

Table I. Karyotype determined in blood samples of patients in gynaecological endocrinology unit of Hospital Clínic of Barcelona.

Karyotype		N Patients (%)
Pure monosomies	45 X0	10 (32%)
Deletions	46XdelX	2 (6%)
Translocations	46,XX t(X;7)(q26:p13)	1 (3%)
Isochromosome	46 X i(X)(q10)	2 (6%)
Mosaicisms		
Pure/XX	Mos 45X0/46XX	3 (10%)
Ring chromosome/XX	Mos 45XrX/46XX	3 (10%)
Pure/isochromosome	Mos 45X0/46XiXq	9 (29%)
Pure/XY	Mos 45X0/46XY	1 (3%)

Table II. Final height of patients in gynaecological endocrinology unit of Hospital Clínic of Barcelona, sorted by karyotype and GH treatment. Average ± SD of height and BMI.

Parameters	GH treatment (n = 15)	No GH treatment (n = 16)	All
45 X0 pure	Height: 143.9 ± 5.1	Height: 145.0 ± 3.0	144.2 ± 4.5[b]
	BMI: 24.9 ± 2.6	BMI: 24.6 ± 3.6	25.3 ± 3.8
(n = 10)	(n = 7)	(n = 3)	
Other[a]	Height: 150.1 ± 4.7	Height: 151.3 ± 9.3	150.9 ± 7.7[b]
	BMI: 23.2 ± 2.5	BMI: 26.5 ± 4.7	24.9 ± 4.0
(n = 21)	(n = 8)	(n = 13)	
All	Height: 147.2 ± 5.7	Height: 150.1 ± 8.7	148.7 ± 7.5
	BMI: 24.0 ± 2.6	BMI: 26.2 ± 4.5	25.1 ± 3.8

[a]The group includes mosaicism, isochromosomes, ring chromosomes, and X-deletions, in monosomy or mosaicism, [b] $p < 0.05$ in *T*-student test.

in our case-series there is a higher percentage of pure monosomy patients treated with GH (7 out of 10) than other karyotypes (8 out of 21).

Two genes have been identified as strong candidates for short stature, SHOX and PHOG, both located in the distal part of the short arm of the X- and Y-chromosomes (Xp11–22, Yp11). Mutations in these genes could also explain some skeletal abnormalities in TS, such as Madelung deformity of the wrist, cubitus valgus or short fourth metacarpal. Haploinsufficiency of SHOX expression could explain other features such as chronic otitis media, prominent ears, and problems learning how to suck, blow, eat or articulate [2].

Lymphoedema is caused by an absence or hypoplasia of lymphatic vessels and is generally identified at birth, improving overtime. Other external physical disorders linked to TS are epicanthus, deformity in the pinna, micrognathia, cleft palate, short neck, pterygium colli, short limbs, low-set ears, cubitus valgus and genu valgum [4]. In our case-series, greater or minor stigmata were observed in 28 out of 31 patients.

Ovarian dysgenesis

Although the gonads in TS differentiate normally until the third month of gestation, an accelerated degeneration of oocytes occurs after this period, with an increase in ovarian stromal fibrosis. Consequently, ovarian failure takes place within the first few months or years of life. Despite the fact that primary amenorrhoea is usual in TS, the incidence of spontaneous puberty is 8% in patients with the 45X0 karyotype, while it is found to be as high as 40% in women with mosaicism [5]. In our series of cases, nine patients had spontaneous menarche, bearing only two of them a pure monosomy (45X0) karyotype.

Concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) are high as early as 5 days of age in infants with TS; although these levels decline afterwards, FSH and LH levels remain higher than in girls with a normal karyotype [6,11].

After the induction of puberty with oestrogens, most females with TS require long-term oestrogen replacement therapy with the aim of preventing osteoporosis, reducing risk factors for atherosclerosis and improving aspects of cognitive function [5,12].

Replacement treatment is recommended with natural oestrogen preparation and to be administered orally or with transdermal patches, taking into account the patient's preference or to avoid first-pass hepatic metabolism. Ethinyl-estradiol presented in contraceptive pills has been associated with adverse effects on liver enzymes, lipid metabolism and blood pressure, both in women with normal and Turner karyotype. In addition, some TS females are symptomatic during the pill-free week because of the complete lack of oestrogens.

Progestagen should be given for a minimum of 10 days per month in order to prevent endometrial carcinoma, even though a continuous regimen would avoid menstrual bleeding.

Oestrogen deficiency causes bone loss, endothelial dysfunction, decreased insulin production, an abnormal lipid pattern, increased central adiposity and early atherosclerosis. In oestrogen deficient females with TS, replacement therapy improves liver enzyme abnormalities and some cognitive deficits (reaction time, non verbal processing speed, short-term memory [13]). Therefore, the use of oestrogen replacement up to physiological doses should be maintained until the expected age of menopause. Nonetheless, it is important to emphasize that neither the risk of breast cancer nor that of ovarian

or endometrial cancer is higher in these patients than in the general population [6].

In up to 6% of TS patients the karyotype includes the Y-chromosome, which may lead to the development of gonadoblastoma, a malignant neoplasm composed of stromal and germ cells. Hence, early prophylactic excision of the gonads is recommended in TS women, considering that the risk increases with age (from 2% at age 10, to 27.5% at 30 years [5]).

Concerning options for fertility, spontaneous pregnancies occur in less than 5% of TS patients, with the risk of the development of congenital malformations or chromosomopathies. Oocyte donation and *in-vitro* fertilization should be recommended because most of women with TS are infertile. Nevertheless, the risk of first trimester miscarriage is higher, probably due to uterine hypoplasia and some uterine ischaemia during pregnancy [11,14,15]. Caesarean rates are higher due to cephalopelvic disproportion resulting from their body habitus. Among the 31 patients of the present case-series, only two had children by oocyte donation. The delivery was performed by caesarean section due to cephalopelvic disproportion.

TS is associated with many cardiovascular disorders and as such, cardiac assessment, including echocardiography and strict blood pressure monitoring should be recommended before the application of assisted reproductive techniques.

Finally, prenatal diagnosis of TS allows the prediction of gonadal insufficiency in women demonstrating early evidence of ovarian function; hence, new techniques of ovarian tissue cryopreservation with the aim of replantation may be suitable for a few selected females with TS.

Osteoporosis

Short size and osteoporosis could be due to a primary defect in bone formation. Although this molecular defect remains to be identified, some genes situated in X-chromosome are associated with connective tissue changes [16].

A reduction in peak bone mass by 25% has been described in women with TS. Nonetheless, bone density measurements depend on height, and short size and GH treatments in TS may be confounding factors. However, the incidence of fracture in girls and adult women with TS is three-fold higher than in normal controls [17].

GH treatment for at least 1 year, together with oestrogen replacement started before 12 years of age, improve bone mineral density. Indeed, girls with TS and spontaneous menarche have been found to achieve normal bone mass [18].

Among the patients included in this case-series, those who received treatment with GH during infancy presented osteoporosis or severe osteopenia in eight and five cases respectively. At present, three are receiving calcium and the other three bisphosphonates. On the other hand, eight patients who did not receive GH were diagnosed with osteoporosis; three take calcium and one bisphosphonates.

Cardiovascular disease

Along with all the alterations described above, cardiovascular complications are the main cause of increased mortality in TS, in which life expectancy may be reduced by up to 13 years. Dilatation of the root of the aorta, hypertension, and bicuspid aortic valve have been reported as major cardiovascular complications in TS [19]. In addition, mortality due to ischaemic heart disease is increased up to seven-fold in women with TS, although the precise mechanisms of increased cardiovascular risk in TS are unclear [19].

Despite cardiovascular complications in TS being mainly associated with hypogonadism, and a consequent decrease in oestrogen production [20], differences in X-chromosome gene expression may also contribute to these complications. Several genes implicated in the control of cardiovascular function have been described in the X-chromosome, including the angiotensin type 2 receptor and several kinases and transcription factors [21].

Bicuspid aortic valve is the most common congenital malformation (16%) and, although it is usually an isolated abnormality, it may occur together with other anomalies such as aortic coarctation. This combination may result in progressive valvular dysfunction due to calcification in the aortic valve and may cause aortic stenosis or regurgitation in adulthood. Coarctation of the aorta affects 10% of women with TS causing hypertension and seems to be more associated with severe lymphoedema, perhaps due to abnormal lymphatic flow by compression of the ascending aorta [2,22].

Other abnormalities, such as partial anomalous venous drainage and mitral valve prolapse are more common among TS women, and left-side cardiac anomalies are associated with endocarditis, with prophylactic antibiotics being essential before surgical procedures.

However, the most serious risk for females with TS is aortic dissection, which may occur at any age causing even sudden death. Accordingly, echocardiography should be included in the assessment of TS patients and should be indicated periodically. Electrocardiogram should be carried out along with the imaging studies because conduction or repolarization defects have been reported attributed to neuroautonomic dysfunction [2].

Hypertension, a bicuspid aortic valve and dilated aortic root (with an age-related increase of the root diameter greater than the normal population) are risk factors for dissection, making antihypertensive treatment in women with two of these three disorders advisable [23].

In this case-series, three patients were diagnosed with congenital bicuspid aortic valve, all involving the 45X0 karyotype. In addition, one patient had mitral prolapse, and two more had acquired valve insufficiency. Five patients present high blood pressure for which they were receiving antihypertensive treatment.

Metabolic abnormalities

Patients with TS have a higher prevalence of other subrogate cardiovascular risk factors such as dyslipidemia and diabetes mellitus due to insulin resistance [5]. Type 2 diabetes mellitus is 2–4-fold more common in women with TS, and an early metabolic defect in glucose uptake has been described. Insulin resistance and secondary hyperinsulinemia do not seem to be dependent on the body mass index, as in the polycystic ovarian syndrome, but obesity and an elevated waist-to-hip ratio found in TS worsen this defect. Moreover, hypertriglyceridemia may be a consequence of hyperinsulinemia and obesity.

Hypercholesterolemia has been described at the expense of an increase of low-density lipoproteins followed by a decrease of high-density lipoproteins. GH therapy aggravates this disorder, but the effect is reversible after discontinuation of the treatment [24].

Liver enzymes are often raised in females with TS, but this seems to be a transient and benign dysfunction. However, these patients have a five-fold increase in the risk of cirrhosis [1]. Hence, liver function should be checked periodically.

The main metabolic parameters including glucose-insulin, lipids and liver enzymes are shown in Table III as is the number

Table III. Carbohydrate, lipid and hepatic profile patients ($n = 31$) in gynaecological endocrinology unit of Hospital Clinic of Barcelona.

Parameters	Average ± SD	Number of patients above normality limit
Carbohydrate profile		
Glucose	77.4 ± 12.3	1[a]
Insulin	9.0 ± 5.6	3
Lipid profile		
Cholesterol	196.2 ± 36.5	2[b]
HDL-cholesterol	63.7 ± 14.4	0
LDL-cholesterol	116.2 ± 30.8	0
Triglycerides	77.5 ± 29.2	0
Hepatic profile		
ASAT[c]	32.8 ± 22.4	6
ALAT[d]	39.8 ± 32.6	9
GGT[e]	96.9 ± 138.7	15
Alkaline phosphatase	235.6 ± 130.8	10
LDH[f]	423.5 ± 61.9	8

[a]Patient diagnosed of Diabetes Mellitus type II. Receiving treatment with metformin.
[b]One of the cases belonged to the group of nine patients receiving statins for previous hypercholesterolemia. The other one has never been treated for hypercholesterolemia.
[c]ASAT, alanine transaminase.
[d]ALAT, aspartate transaminase.
[e]GGT, γ-glutamil transferase.
[f]LDH, lactate dehydrogenase.

of patients outside the range of the normal limits. One patient was treated with metformin due to type 2 diabetes mellitus, and another presented glucose intolerance. Ten patients were diagnosed with hypercholesterolemia and were receiving statins. Up to 50% of patients had an alteration of at least one liver parameter (Table III).

In conclusion, close control of blood pressure, as well as a yearly determination of the lipid, carbohydrate and hepatic profiles should be included in the correct assessment of TS women in adulthood.

Immunological disorders

Hypothyroidism affects up to 70% of TS patients, especially due to autoimmune causes, and a mild and transient TSH elevation without thyroid autoantibodies has been observed. Thyroid function should be checked annually in order to diagnose the development of hypothyroidism early.

Fourteen patients in the present series were diagnosed with hypothyroidism and were receiving thyroid hormone. Furthermore, increased levels of antiperoxidase and antithyroglobuline antibodies, respectively, were detected in another 19 and 12 patients.

Indeed, autoantibodies and consequently, autoimmune diseases, such as coeliac disease, inflammatory bowel disease, *vitiligo* and *alopecia areata*, adrenal insufficiency, juvenile idiopathic arthritis or type 1 diabetes mellitus, are increased in these patients [25–27]. A region in the X-chromosome where the foxp3 gene, which defines IPEX syndrome may be found, has been linked to these autoimmune disorders. FoxP3 expression correlates with CD127 low leucocytes (leucocytes with low CD127 expression [28]), and it has been suggested that the same alteration may justify an increase in the prevalence of autoimmunity in TS, especially among isochromosome karyotypes [28].

It has also been suggested that other immune disorders may be present in TS patients; for instance a low CD4/CD8 ratio or a low concentration of immunoglobulins. Despite these alterations, an increase in infections has not been described, with the exception of otitis media [28,29].

Sensorineural disorders

TS females show conductive hearing loss as a consequence of several episodes of otitis media. The main cause for this loss is the deformity in the pinna, yet an impaired immune system may play a key role as well. Furthermore, two different sensorineural patterns have been observed in audiometry, one showing dips at high frequency and the other at middle frequency. Disorders in other objective tests such as brain auditory evoked potentials may also be observed [30].

In the present series, almost 50% of patients attended in the Gynaecological Endocrinology Unit in the Hospital Clinic showed different degrees of hypoacusia evaluated by audiometry.

Regular audiometric checks should be performed referring patients to ENT departments.

Psychosocial development

Although there are exceptions, intelligence is within the average range in most females with TS, with good verbal skills. However, some have difficulties with non verbal learning disabilities, including number work, visuospatial and perceptual abilities and motor coordination. Moreover, parents report a reduced concentration span with less short-term memory. Again, the severity of the cognitive impairment is linked with the karyotype, being worse in pure monosomy than mosaic patterns [23]. Differences in brain structure, including smaller parietal lobes, parietalocipital and prefrontal volumes correlate with differences in brain functions [31].

Furthermore, women with TS have some personality traits, with greater difficulty in making friends and entering into sexual relationships. Although the difficulty in non verbal communication may have a role, poor self-image as a result of short statue, dysmorphology and delayed sexual maturation may be the main cause.

Females with TS should have access to clinical psychologists for counselling related to anxieties and for working to improve specific areas of deficiency. Families should have support in obtaining appropriate therapy, including special accommodations at school [2].

Other disorders

Congenital renal disorders are nine-fold more common in women with TS than in the general population[5]. These abnormalities include horseshoe kidney, duplex systems and rotated kidneys. Malformations are more common in 45X0 monosomy females, being related to neither hypertension nor other clinical symptoms. Nevertheless, renal ultrasound is recommended at diagnosis and should be repeated at the time of adult transfer.

In this case-series of the Hospital Clínic, six patients showed renal malformations on ultrasound: three with horseshoe kidney, two with duplex systems, and one with rotated kidneys. Only one had pure monosomy in the karyotype. Figure 2 shows images of these congenital renal disorders.

The most common ocular findings linked to TS are strabismus, ptosis and amblyopia. All patients should have eye assessment carried out during follow-up if required.

Conclusions

To conclude, females with TS have a high risk of developing medical problems, from infancy to adulthood. After early
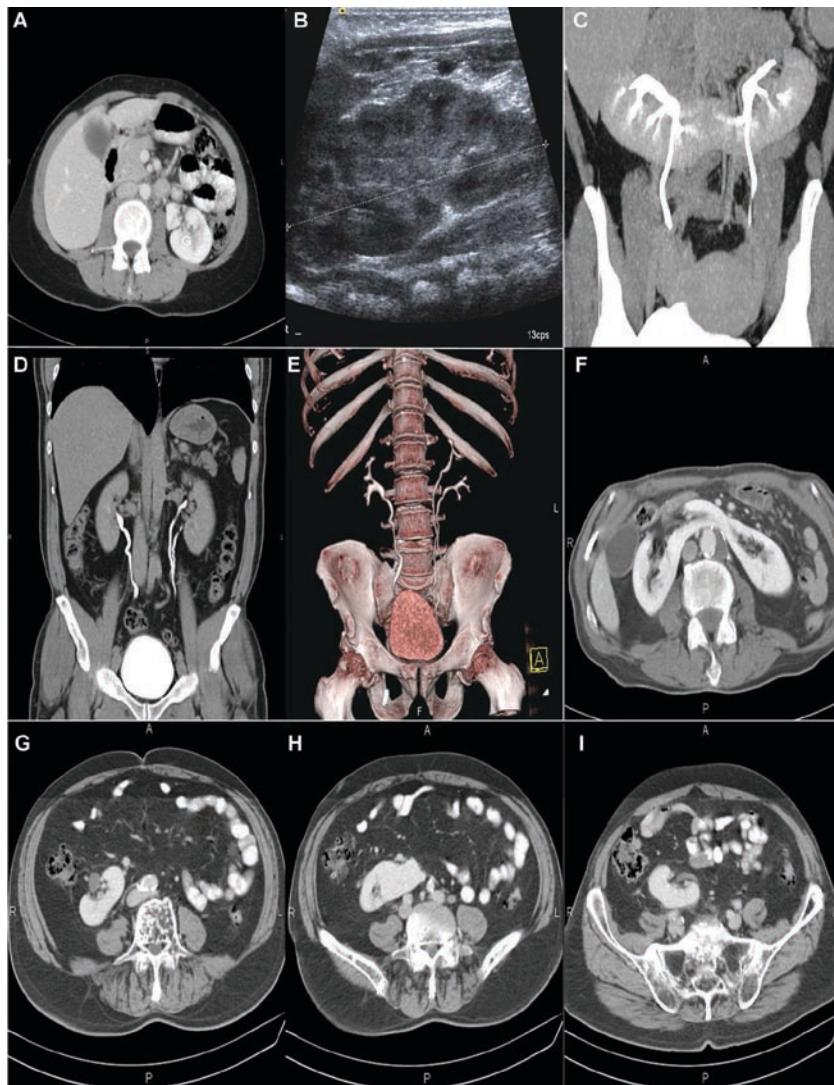
Figure 2. Main renal malformations associated with Turner's syndrome. (A) Axial plane of an abdominal TC showing a right renal agenesia. (B) Abdominal ultrasound showing a compensatory right renal hypertrophy in a newborn with unilateral agenesia. (C) Coronal CT-urography reconstruction showing a horseshoe kidney. (D) & (E) Coronal CT-urography reconstructions showing a duplex system of the left kidney. (F) Axial plane of a CT showing a horseshoe kidney. (G), (H) & (I) Three different axial CT planes of the same patient showing renal malposition, being both kidneys on the right side.

diagnosis, they should be followed by a multidisciplinary team of specialists to control the comorbidities associated with this syndrome.

At first, specialized paediatricians should perform a congenital malformation screening, with echocardiography and renal ultrasound. In this period, it is recommended to follow guidelines for the treatment with GH, as well as oestrogen replacement for correct sexual development.

In adulthood, these females should be followed in specialized endocrinological-gynaecological units to diagnose disorders which debut in adulthood, such as metabolic, immunological and sensorineural disorders. Hormone replacement treatment should be guaranteed, as should reproductive and sexual advice.

Some studies from France [3], Belgium and the United States [32,33] have reported that only a small minority of females (approximately 3.5%) with TS are transferred to an adult service that provides health assessment according to international guidelines. Several aspects of these recommendations are controversial: how to optimize screening evaluations, which cardiac

malformations contraindicate assisted pregnancy, the best options for hormone replacement therapy and when to use them, or the evaluation of the influence of GH.

It should be highlighted that a small number of studies of TS patients in adult life have been published. Furthermore, gynaecologists follow TS women in adulthood and usually a lack of paediatric data exists, hindering patient's complete evaluation. Finally, patients from different ages have been managed following different protocols, due to the improvement of the prenatal or early diagnosis. This fact hampers the evaluation of our case-series and others included in the systematic review.

Although partial correlation between phenotype and karyotype has been observed in our case-series, the possibility of a link between karyotypes and clinical features suggests a novel hypothesis to explain the different phenotypes and clinical abnormalities observed in these patients. Until now, chromosomes in peripheral blood samples are the main source of data. Perhaps, analysis of karyotypes with cells from other embryological tissues could provide new orientations.

Therefore, research into these areas of uncertainty is needed to improve the follow-up of TS females.

Acknowledgements

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2. COMPARATIVE CYTOGENETIC ANALYSIS IN TWO TISSUES WITH DIFFERENT LINEAGE IN TURNER'S SYNDROME PATIENTS. CORRELATION WITH PHENOTYPE.

Article sotmès a l' ***American Journal of Obstetrics and Gynecology.***

Cobrint tot l'espectre de l'especialitat, ***American Journal of Obstetrics and Gynecology***, "The Gray Journal", presenta els últims procediments de diagnòstic, investigació d'avantguarda i comentaris d'experts en medicina maternofetal, endocrinologia reproductiva i infertilitat, i ginecologia oncològica, així com d'obstetrícia i ginecologia general.

Impact Factor (IF): 3.468; mitjana de l'IF dels últims 5 anys: 3.560. Es troba al primer decil de l'especialitat d'Obstetrícia i Ginecologia (posició 9/79), d'acord amb el Journal Citation Reports 2011®.

COMPARATIVE CYTOGENETIC ANALYSIS IN TWO TISSUES WITH DIFFERENT LINEAGE IN TURNER'S SYNDROME PATIENTS. CORRELATION WITH PHENOTYPE.

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CONDENSATION:

Analysis of karyotypes of Turner's syndrome patients in two tissues of different lineage,

and to correlate them with phenotype.

SHORT VERSION OF THE TITLE:

Cytogenetic analysis in Turner's syndrome patients.

ABSTRACT

Objective: to analyze karyotype of Turner's syndrome (TS) patients in two tissues of different lineage, and to correlate them with phenotype.

Study design: an observational study was designed at the Gynaecological Endocrinology Unit of Hospital Clinic in Barcelona. Patients diagnosed with TS by blood karyotype were included, between 20-50 years of age. A new 50-cell count blood karyotype and a urethral cell karyotype from urine samples were performed. Data on some TS-related comorbidities were collected.

Results: Twenty-seven TS patients were included. Urine cultures of 12 patients were contaminated by microorganisms. With 50-cell count blood karyotype, 3 cryptic mosaicisms were found. Six patients with mosaicism in blood karyotype showed pure monosomy in urine karyotype. Correlations exist between blood karyotype and phenotype where spontaneous menarche, height, dysmorphology, congenital malformations and hypothyroidism are concerned, whereas they did not appear in urine analysis.

Conclusions: Karyotyping T-lymphocytes in blood samples is the gold standard technique. 50-cell count may be considered if TS or ovarian failure is suspected, in order to detect cryptic mosaicisms. Urethral cell culture from urine samples presents technical difficulties and some limitations, due to the easier lost of abnormal X-chromosome that worsens its correlation with phenotype. A partial correlation between blood karyotype and phenotype exists.

Keywords: cytogenetic analysis, Turner's syndrome, karyotype, phenotype.

INTRODUCTION

Turner's syndrome (TS) is defined cytogenetically by the monosomy of the X-chromosome (45,X), the presence of an abnormal X-chromosome, or the mosaicism combining 45,X in a cell line with an abnormal X-chromosome in another cell line [5]. X-chromosome inactivation, called lyonization, takes part in the early embryogenesis stages in women with normal karyotype. Consequently, only one X-chromosome is active in each diploid cell. This process usually occurs in a random manner [6]. However, if there is an abnormal X-chromosome, this will be preferentially inactivated. Lyonization is controlled by XIC (X chromosome inactivation center), and if the X-chromosome presents a deletion including locus XIC, it may not be inactivated [7].

Some regions of the X-chromosome are not inactivated and thus the genes of these regions show a diploid expression [8]. These are the pseudoautosomal regions (PAR) located at the ends of the chromosome (PAR1 at Xpter and PAR2 at Xqter) which usually work disomically, since both copies are essential for normal development [9]. It is hypothesized that TS phenotype is due to the haploinsufficiency of these genes. This hypothesis is based on the fact that 31 out of these 34 not inactivated genes are found in the short arm of the X-chromosome, and a deletion of this arm is closely related with TS phenotype [14].

A certain correlation between cytogenetics and phenotype in TS has been established [4,16,14], with pure monosomy of X-chromosome being the most common karyotype and the one related with the most characteristic phenotype: short stature, swelling and gonadal dysfunction with primary amenorrhea [15]. Conversely, over 40% of women presenting mosaicism have spontaneous menarche prior to developing gonadal dysfunction [10]. Nevertheless, there is no predictable correlation between genotype and phenotype [14].

Around 99% of pregnancies that show 45,X karyotype end up in a spontaneous miscarriage during early embryogenesis [11]. This high percentage of abortion leads to the idea that a certain degree of mosaicism for fetus survival may in fact be necessary, even if the mosaicism is with a second line of cells that have a partially deleted X-chromosome [11, 12, 13]. Detection of cryptic mosaicism can be influenced by four factors: types of tissues analyzed the number of cells studied, technique sensitivity and the proportion of each cell line. The combination of these factors determines the likelihood of successfully detecting the mosaicism. Thus, in those patients with low percentages of aneuploidy, the standard analysis of 15 or 30 cells may not be sufficient to detect mosaicisms. The present study has therefore been designed to analyze the karyotype of previously diagnosed TS patients in two tissues of different lineage, T-lymphocytes (mesoderm) and urethra epithelial cells (endoderm). Additionally, the number of cells analyzed was rounded up to 50. The goal of the study is to analyze whether there are differences in the results of the karyotype between two different tissues, and to correlate the new karyotypes with the clinical features of the patients.

MATERIAL AND METHODS

Patients

Patients between 20 and 50 years old with Turner's syndrome monitored at the Endocrinological Gynaecology Unit of the Hospital Clinic of Barcelona were recruited between June 2010 and June 2011. The patients' diagnosis had initially been performed during infancy due to the appearance of gonadal dysfunction or characteristic TS features. Karyotype of 15-30 blood T-lymphocytes had been analyzed to consider TS if more than 10% of the cells bore an altered X-chromosome.

Additionally, other variables were evaluated: age, anthropometric characteristics, spontaneous menarche and age at diagnosis. The presence of phenotypic dysmorphology described in TS patients (epicanthus, ocular ptosis, strabismus, deformity in the pinna, micrognathia, cleft palate, short neck, *pterygium colli*, limbs lymphedema, *cubitus valgus*, *genu valgum*, low-set ears or low hair implantation, syndromic facies) were examined. TS-associated cardiac and renal malformations were also recorded, and subsequently evaluated by echocardiography and abdominal ultrasonography. Finally, hypothyroidism was diagnosed through the detection of antithyroid antibodies and alteration of thyroid hormones in blood analysis.

Blood chromosome sampling

New blood sample was obtained for each patient in order to analyze 50 T-lymphocytes karyotype. T-lymphocytes karyotype was performed following the standard procedure. Briefly, blood sample was incubated in PB-Max (Gibco) culture medium for two days. Cells were then treated for 30-60 minutes with colcemid (Invitrogen) to arrest cells in metaphase. These were subsequently treated with hypotonic solution to lyse cell membranes.

Urine chromosome sampling

In order to analyze 50 urethra epithelial cells, urine sample was obtained by spontaneous micturition. These cells are found in urine coming from urethral descamation. Urethra epithelial cells karyotype was performed following the standard procedure. Briefly, urine sample was cultured for 3-4 weeks in Chang D medium (Irvine Scientific) completed with streptomycin, penilicilin and fungizone just after urine sample collection. Cells were then treated for 4 hours with colcemid (Invitrogen) to

arrest cells in metaphase. Again, these were subsequently treated with hypotonic solution to lyse cell membranes.

Chromosome analysis

Chromosomes were fixed using methanol-acetic 3:1 solution and stained with Wright dye (Sigma). Metaphase screening was conducted on the Metafer platform (Metasystems), using Ikaros software (Metasystems) to analyze chromosome abnormalities.

Sub-groups analysis

Height, dysmorphology, the presence of congenital cardiac and/or renal malformations, spontaneous menarche and hypothyroidism were analyzed comparing two sub-groups of karyotypes. The first group included patients with pure monosomy or pure long arm isochromosome, in accordance with the hypothesis that the vast majority of genes related to TS phenotype are located in the short arm of the X-chromosome [14]. The second group included the rest of TS karyotypes (other X-chromosome alterations or mosaicisms). Exceptionally, when hypothyroidism analysis was performed, patients were divided according to the presence of isochromosome in the karyotype, in pure line or mosaicism. A correlation between long arm isochromosome and autoimmune hypothyroidism is supported in literature [70].

Ethical considerations

The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona and all patients were informed about the study and the interventions that would be

performed. Signed informed consent was obtained from all patients at the time of their inclusion.

Statistical analysis

For all continuous variables, average and standard deviation were calculated, and U Mann-Whitney test was used to compare groups. For categorical variables a goodness of fit test was performed to compare groups. The binomial distribution was used to obtain the likelihood of non 45,X cell detection in patients with mosaicism.

RESULTS

Twenty seven patients with TS agreed to being involved in the present study. These patients had a mean age of 36.9 ± 7.5 years, a Body Mass Index (BMI) of 24.9 ± 4.0 kg/m^2 and a height of 149 ± 8 cm. The mean age of TS diagnostic was 11.1 ± 10.5 years, and eight patients (29.6%) showed spontaneous menarche. Five patients (18.5%) presented congenital cardiac malformations, six patients (22.2%) bore congenital renal malformations, and 13 (48.1%) were diagnosed with autoimmune hypothyroidism.

The outcomes of paediatric blood karyotype, new 50-cells count blood karyotype, and urine blood karyotype are shown in Table I. The karyotype of urethral epithelium was missing for 12 patients due to culture contamination (by fungi or cocci) and the lack of opportunity to obtain new samples. Furthermore, 50-cell metaphases could not be analyzed in all urine samples due to low cell concentrations.

According to paediatric blood karyotype, ten patients presented pure 45,X monosomies, twelve patients bore a mosaicism, and five more patients had an altered X chromosome in pure line, two of them being an isochromosome of the long arm. When 50 T-lymphocytes were counted, 3 of the patients (number 8, 25 and 27) with a previous pure monosomy, showed a cryptic mosaicism. The percentage of 45,X was 94%, 98% and

94% respectively. The likelihood of detection of low proportion cell line in a TS patient with mosaicism is depicted in table II and in relation with the number of metaphases analyzed. For instance, if 15 metaphases are analyzed, there is less than a 50% chance of identifying the mosaicism when the actual percentage of 45,X in the patient is 95%. This chance rises up to 92% when 50 cells are analyzed (Table II).

Only two urine samples of patients with pure monosomy in blood karyotype could be analyzed, with monosomy also being revealed in urethral cells. However, six patients with mosaicism in blood karyotype showed pure monosomy through urine karyotype. These chromosomes (not found in urine) were ring-X chromosome in 2 patients, isochromosome-X in three patients (the 46XX line was also not found in one of them) and isodicentric-X in the last patient (Table I). Therefore, monosomies 45,X were more frequently found in urethral cells than T-lymphocytes from blood samples (Figure 1).

Sub-analysis to take into account the relation between karyotypes and phenotypes was performed. The average height of patients with pure monosomy or pure isochromosome in the new blood karyotype was 143.1 ± 4.1cm, compared to 152.2 ± 8.2cm for the remainder of patients. The differences between both groups were statistically significant (p=0.014). Conversely, no differences were found between height when groups with the same karyotype according to urine samples (p = 0.92) were examined, noting that the height of the remainder of patients with pure monosomies and pure isochromosomes were 150.7 ± 9.5cm and 151.2 ± 8.6cm. Finally, similar results to the pure monosomy group have been observed in the three patients with cryptic mosaicism found in the new karyotype (147.0 ± 7.2 cm; p=0.51). It should also be noted that patient number 14 has reached a height of 170 cm, with an isodicentric X-chromosome.

Similarly, statistical differences were found between both sub-groups when the presence of TS stigmata was considered. All patients with a pure monosomy or isochromosome

in blood karyotype presented some degree of dysmorphology, whereas 34% of the remaining patient group did not (p=0.03). The three patients with new cryptic mosaicism presented TS stigmata.

Only one patient diagnosed with pure monosomy or isochromosome (8%) had spontaneous menarche. Conversely, 47% of patients in the second group presented spontaneous menses and pubertal development until the onset of ovarian failure (p=0.01). This time, the three patients with new cryptic mosaicism presented spontaneous menarche, reversing the significant differences between groups (p=0.09).

Huge differences were found between both groups considering the presence of cardiac or renal congenital malformations. Eight out of 12 patients in the group with pure monosomy or isochromosome presented congenital malformations, whereas only 2 out of 15 of the other group did (p<0.000001). Two patients with new cryptic mosaicism showed malformations.

Hypothyroidism was analyzed comparing patients with isochromosome (in pure line or mosaicism) and the rest of karyotypes. Up to 89% of patients with hypothyroidism showed a line of isochromosome in their blood karyotype, while only 28% did in the second sub-group (p<0.0001).

Finally, no differences in the incidence of dysmorphology, primary amenorrhea or congenital malformations between monosomy-isochromosome TS patients and other TS karyotypes were observed when urine samples were analyzed (70% *vs* 60%, 60% *vs* 40% and 80% vs 80% respectively).

COMMENT

The main findings of the present study are: 1) technical limitations of urine culture exist and this cannot be considered as a standard technique to analyze karyotype; 2) counting from 35 to 50 metaphases is recommended when TS is suspected; and 3) a correlation

between phenotype and blood karyotype exists, although this has not been revealed with urethra epithelial cells.

The analysis of a tissue of different lineage of T-lymphocytes, such as urothelial cells, may be complementary in the study of chromosome abnormalities. Urine sampling is non-invasive and is easy to administer for the purposes of obtaining a culture. Nevertheless, some technical limitations should be considered. First of all, it is essential to mix the urine with Chang D Medium immediately after the sample collection to dilute urine acidity. In addition, the first centrifugation should occur less than 1 hour following the sample collection. The sample is also susceptible to contamination by microorganisms during the 3-4 necessary weeks required for the culture to develop. Blood culture is faster, and blood samples are frequently ordered to analyze other altered parameters related to TS [14]. In the present study, up to 44% of urine samples were lost due to contamination, and 50 cell metaphases could not be analyzed in all urine samples due to low cell concentration. Urine chromosomes provide lower resolution of the bands, and consequently, karyotype is more difficult to obtain. Therefore, urine culture is not recommended at this stage as a standard technique to analyze karyotype, and blood samples remain the gold standard.

In studying karyotype 15 or 30 metaphases are usually counted for standard blood analysis. Following the theory that a mosaicism is necessary for fetus survival [11, 12, 13], a cryptic mosaicism would be easier to detect counting from 35 to 50 cells. In the present study, 3 patients with previous 45,X monosomy showed a cryptic mosaicism when the number of cells were increased to 50. A line of isochromosome was revealed in patient number 25, which could strengthen her hypothyroidism; three metaphases with ring-X chromosome were expressed in patient number 27. However, the most interesting patient was the cryptic mosaicism of patient 8, where three metaphases with

46XY appeared after counting 50 cells. A bilateral gonadectomy was therefore performed, owing to the risk of gonadoblastoma described in females with lines which contain Y chromosome [67]. Nevertheless, 50-cell count is particularly interesting in the study of women with occult or premature ovarian failure, who often consult in connection with fertility/infertility issues. Detection of a cryptic mosaicism with some metaphases with monosomy 45,X may explain their infertility [18].

A greater number of monosomies have been found analyzing urine samples, compared to blood karyotype. It is known that X-chromosome is the most frequently lost in women, and this fact increases with age [68]. Additionally, endoderm cells seem to lose abnormal X-chromosomes more easily than T-lymphocytes. No ring-X chromosome was found in urine in the present study, due to its instability. Neither were any lines of long arm X-isochromosome found among the urine samples. Karyotype information is gathered when urine samples are analyzed and this seems to negatively affect the relation between genotype and phenotype.

Although not absolutely predictable, some correlation exists between blood karyotype and phenotype amid this study group. This correlation did not exist, however, when urine samples were analyzed. Genes responsible for short stature are localized in the short arm of the X-chromosome, and more specifically in the pseudoautosomic regions which escape X inactivation [69]. TS subjects with 45,X monosomy and pure long arm isochromosome have therefore been classified in the same group in the present study, presenting lower height than the remainder. The higher than usual height of the patient with isodicentric X-chromosome should be explained by the triple dose of genes located in the PAR 1, where SHOX-homebox is located. Furthermore, SHOX-homebox is also strongly expressed during embryologic development of extremities, and its alteration may explain some skeletal abnormalities causing dysmorphology features related with

TS [21, 22, 23]. Differences observed between both sub-groups associated with TS stigmata correspond with the literature. Similar results have been found in connection with the presence of spontaneous menarche. Again, critical regions responsible for ovarian failure are also hypothetically located in the distal part of the short arm of the X-chromosome; Xp11, Xp13-25 and Xq26-28 [24, 25].

Cardiac and renal malformations were also present more frequently in those 45,X monosomies analyzed in blood samples. Heart, kidney and gonads are derived from mesoderm germ layer, as well as T-lymphocytes. Conversely, the thyroid gland is derived from endoderm; therefore sub-groups for the sub-analysis were performed according to the presence of isochromosome [4, 16]. No correlation exists with urethral cells, despite the same lineage. This is due to the ease of disappearance of abnormal X-chromosome.

The main limitation of the present study is its small sample size, which was exacerbated following contamination of urine samples. This suggests that the results should be interpreted with caution. However, in this era of metaanalysis, it is useful to provide the results of well-designed studies, even those that have low statistical power. This study is intended to stimulate future larger scale, adequately powered, and probably multicentre trials to further develop the genetic study of TS, analyzing new tissues of third lineage (endoderm) such as in the liver or skin. This may provide the larger basis required for an eventual metaanalysis to help clarify the value of this approach. Secondly, nowadays TS diagnosis is easier and more advanced than 20 years ago, with patients often being diagnosed prenatally or immediately following delivery. Early determination of karyotype is better than the determination possible with this study's patient group, who bore evidence of the loss of abnormal X-chromosome due to age or tissue analyzed.

In conclusion, T-lymphocytes karyotype from blood samples is the gold standard technique for this kind of analysis. However, 50-cell count may be considered if TS or ovarian failure is suspected, in order to detect cryptic mosaicisms. Urethral cell culture from urine samples presents technical difficulties and some limitations, due to the more ready loss of abnormal X-chromosome, which adversely affects its correlation with phenotype. A partial correlation between blood karyotype and phenotype exists, and more research is needed to identify the involvement of genes situated in X-chromosome in TS-related features.

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TABLES

Table I. Results of paediatric previous blood karyotype, new 50-cell count blood karyotype and urine karyotype of each patient of the study. In brackets the number of cell metaphases counted.

Patient number	Previous blood karyotype	New blood karyotype	Urine karyotype
1	45,X	45,X [50]	45,X [50]
2	45,X	45,X [4]	46,X,i(X)(q10) [51]
	46,X,i(X)(q10)	46,X,i(X)(q10) [44]	47,X,i(X)(q10)+i(X)(q10)[7]
		47,XX,+i(X)(q10) [1]	
		47,X,i(X)(q10),+i(X)(q10)[1]	
3	45,X	45,X [41]	45,X [15]
	46,X,i(X)(q10)	46,X,i(X)(q10) [9]	
4	45,X	45,X [46]	45,X [50]
	46,X,i(X)(q10)	46,X,i(X)(q10) [4]	
5	45,X	45,X [25]	45,X [3]
	46,X,i(X)(q10)	46,X,i(X)(q10) [25]	46,X,i(X)(q10) [35]
6	45,X	45,X [32]	45,X [11]
	46,X,r(X)	46,X,r(X) [18]	
7	45,X [7]	45,X [17]	-
	46,X,i(X)(q10) [18]	46,X,i(X)(q10) [33]	
8	45,X	45,X [47]	-
		46,XY [3]	
9	46,XXq-	46,XXq- [50]	46,XX,del(X)(q21) [51]
10	45,X	45,X [38]	45,X [52]
	46,XX	46,XX [6]	
	46,X,i(X)(q10)	46,X,i(X)(q10) [6]	
11	45,X	45,X [45]	45,X [33]
	46,XX	46,XX [5]	46,XX [17]

12	45,X	45,X [50]	45,X [45]
13	45,X	45,X [51]	45,X [50]
	46,X,r(X)	46,X,r(X) [9]	
14	45,X	45,X [16]	45,X [13]
	46,X,idic X (q23)	46,X,idic X (q23)[34]	
15	46,X,i(X)(q10)	46,X,i(X)(q10) [35]	46,X,i(X)(q10) [15]
16	46,XX t(X;7)(q26:p13)	46,XX t(X;7)(q26:p13) [50]	46,XX t(X;7)(q26:p13) [27]
			45,der(X)t(X;7)(q26:p13) [9]
			47,XXX t(X;7)(q26:p13) [12]
17	45,X	45,X [35]	45,X [35]
	46,XX	46,XX [15]	46,XX [2]
18	45,X	45,X [15]	-
19	46,X,i(X)(q10)	46,X,i(X)(q10) [50]	-
20	45,X	45,X [50]	-
21	45,X	45,X [50]	-
22	45,X	45,X [50]	-
23	45,X	45,X [32]	-
	46,XX	46,XX [18]	
24	46,X,del(X)(q13)	46,X,del(X)(q13) [50]	-
25	45,X	45,X [49]	-
		46,X,i(X)(q10) [1]	
26	45,X inv (9)(p11q13)	45,X inv (9)(p11q13) [50]	-
27	45,X	45,X [47]	-
		46,X,r(X) [3]	

Table 2. Likelihood of non 45,X cell line detection when 45,X is in very high proportion.

Metaphases analyzed	Actual percentage of 45,X			
Blood	99%	95%	90%	80%
15	p = 14.0 %	p = 46.3 %	p = 79.4 %	p = 96.5 %
30	p = 26.0 %	p = 78.5 %	p = 95.8 %	p = 99.9 %
50	p = 39.5 %	p = 92.3%	p = 99.5 %	p = 99.999 %
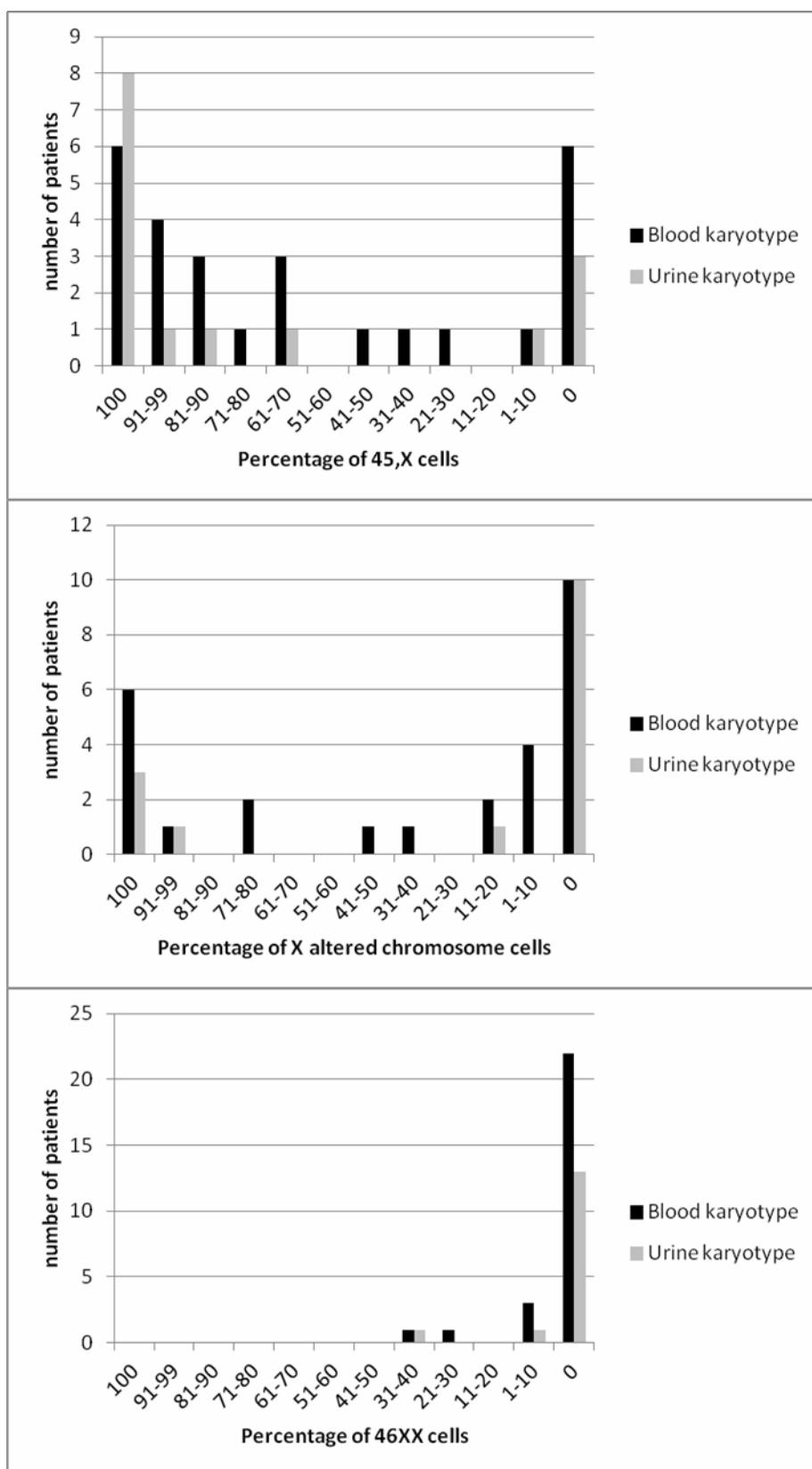
Fig 1. Histogram showing the number of patients with a percentage of (A) 45,X cells (B) X-altered chromosome cells or (C) 46XX cells, in blood or urine karyotype. The histogram was plotted grouping percentages in ranges of 10%.

3. HEARING LOSS IN ADULT WOMEN WITH TURNER'S SYNDROME AND OTHER CONGENITAL HYPOGONADISMS.

Article sotmès a *Maturitas.*

Maturitas és la revista oficial de la Societat Europea de Menopausa i Andropausa. L'àmbit d'aplicació abasta tots els aspectes de la salut postreproductiva en ambdós gèneres, des de la ciència bàsica a l'assistència sanitària i social. *Maturitas* publica sobre les següents àrees: predictors, efectes i tractament de les malalties cròniques; deficiència d'esteroides sexuals en ambdós sexes; epidemiologia, atenció sanitària i social; avenços terapèutics; i medicina complementària i alternativa. Per tant, la revista va dirigida principalment a ginecòlegs, endocrinòlegs, geriatres, andròlegs, sociòlegs i psicòlegs.

Impact Factor (IF): 2.767; mitjana de l'IF dels últims 5 anys: 2.320. Pertany al primer quartil de l'especialitat d'Obstetrícia i Ginecologia (posició 13/79).

HEARING LOSS IN ADULT WOMEN WITH TURNER'S SYNDROME

AND OTHER CONGENITAL HYPOGONADISMS

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ABSTRACT

Objectives: To define the patterns and causes of hearing decline associated to Turner's syndrome (TS).

Study design: An observational study with three cohorts of women was designed: 31 TS patients, 15 women with other congenital hypogonadims (OCH) and 41 healthy age-matched women taking contraception.

Main outcome measures: Clinical history, microotoscopy and standard pure-tone audiometry were carried out on all patients. Brain auditory evoked potentials (BAEP) were performed to all women with hypogonadims (TS and OCH), all of them taking hormone replacement therapy.

Results: Up to 87% of TS subjects suffered from some degree of hearing loss in the audiograms, compared with 20% OCH and 27% controls. Sensorineural hearing loss (SNHL) was the most frequent type of hypoacusia found in TS group, and this was more severe than controls or OCH. BAEP study demonstrated that 61% of TS women showed HL compared to 20% in OCH patients. No significant differences in latencies, amplitudes, and interpeaks of waves I, III and V were found between TS and OCH, nor when compared to reference population. Worse results were observed among the oldest TS patients, those with pure monosomy or isochromosome, and those with a history of recurrent otitis.

Conclusions: More than a half of TS females presented HL in pure-tone audiometry, confirmed by BAEP. Sensorineural type is the most frequent pattern of HL among middle-aged women with TS. Old age, altered karyotype and a history of recurrent otitis are predisposition factors to produce HL among TS patients, while oestrogens play a minor role.

Key Words: Turner's syndrome; Congenital hypogonadisms; Hearing loss; Pure-tone audiometry; Brain auditory evoked potentials.

1. INTRODUCTION

Turner's syndrome (TS) is one of the most common human genetic disorders, occurring in approximately 1:2500 live females. Affected subjects have a wide range of problems associated with loss of an entire sex chromosome or a portion of it, specially the distal part of the short arm. Gonadal dysgenesis and short stature are the main characteristics of TS. However, other medical conditions such as cardiovascular abnormalities, hypothyroidism, osteoporosis and non-verbal learning disabilities are linked with this syndrome [1, 2; 3].

In addition, sensorineural disorders, such as smell alterations [4] or hearing loss have been reported in some patients with TS [0,6,7,8,9]. Young and middle-aged women with TS have a progressive type of hearing impairment, deteriorating rapidly in old age. The conductive hearing loss seems to be a consequence of repeated episodes of otitis media during infancy. The cause for the infection is related to the deformity in the pinna, which is more pronounced in patients with a total delection of the short arm of the X chromosome, as monosomy 45X0 or isochromosome [10]. Two patterns of sensorineural hearing decline in TS patients have been defined: a mid-frequency dip, and a high frequency loss resembling age-related hearing impairment (early presbyacusia) [6, 9, 10]. Therefore, the conductive loss may have a genetic origin, while the pathophysiology of sensorineural lesions is not yet fully understood. Some studies

indicate that cochlear dysfunction is the cause of the sensorineural impairment, and it is potentially influenced by oestrogen deficiency (9, 11).

The relation between otologic disease and karyotype [10,12], the impact of growth hormone treatment and oestrogen deficiency on hearing [11, 13, 14], the physiopathology of the sensorineural hearing loss, or the identification of otolaryngologic markers for the early diagnosis of TS [15], are questions pending resolution.

The aim of the present study was to define the patterns and causes of hearing decline associated with TS, using subjective and objective diagnosis tools. Remarkably, to the best of our knowledge, no previous studies exist where TS women have been compared with other congenital hypogonadisms (OCH) in terms of hearing loss. The current investigation was therefore undertaken to deal with this issue using TS patients, but also two appropriate comparator groups: OCH and a reference control group taking exogenous hormones.

2. METHODS

2.1. Study design and population

Three independent cohorts were selected in the present study:

2.1.1. Turner's syndrome group (TS)

The first cohort corresponds to TS patients (n=31) recruited by the Gynaecological Endocrinology Unit at the Hospital Clinic of Barcelona. The diagnosis of TS was

confirmed by blood karyotype showing a total or partial absence or alteration of X chromosome in at least 10% of cells. Inclusion criteria were TS subjects between 20 and 50 years of age and receiving hormone replacement treatment.

2.1.2. Other congenital hypogonadisms group (OCH)

A second cohort was composed of women with congenital hypogonadism and wild-type karyotype (n=15), receiving hormone replacement treatment. This cohort includes subjects with pure gonadal dysgenesis (hypergonadotrophic hypogonadism), and with idiopathic hypogonadotrophic hypogonadims. The aim of focusing on this group was to define the role of congenital hypooestrogenism in hearing decline associated with TS. Kallmann's syndrome patients were excluded because of its possible association with sensorineural hearing loss [16].

2.1.3. Reference control group

The third cohort included non-exposed age-matched cases (n=41), all of them treated with oestrogens and progestagens for contraceptive purposes. They were recruited by the gynaecological department, none of them taking any other drug that may alter the study results. Animal (17, 18, 76) and human (20, 21, 77) studies indicate that oestrogens could have an impact on hearing. Moreover, cyclical hearing alterations have been described in women with normal menstrual cycle. High pure-tone thresholds have been found during the menstrual phase, when the levels of circulating oestrogens are at their lowest [14, 23]. This was not seen in women using oral contraceptives. Therefore,

a control group receiving exogenous hormones was selected for the present study in order to mimic as far as possible the hormone status of the main study group.

Exclusion criteria were the presence of acute or chronic pathologies non-related with the syndrome being studied which could interfere with the analysis, such as head injury, Meniere's disease or symptoms suggestive of cerebellopontine angle or intracanalicular tumors [11]. The study protocol was reviewed and approved by the Ethics Committee of the Hospital Clinic of Barcelona, and it was performed in accordance with the Helsinki II Declaration and the ICH Guidelines for Good Clinical Practice. All patients were informed about the study and the interventions that would be performed, and signed informed consent was obtained from all of them at the time of inclusion.

2.2. Interventions

Clinical history: blood karyotype, age at diagnosis of hypogonadism, previous history of growth hormone (GH), and oestrogen treatment data were collected. Patients with spontaneous menarche before 16 years of age (and consequently, spontaneous development of secondary sexual characteristics) or patients diagnosised as such before 16 years of age (and consequently, with the beginning of oestrogen replacement therapy before 16 years of age) were considered as having normal puberty. Patients' ENT history was also recorded, including recurrent episodes of otitis media, eardrum tube insertion, tonsillectomy and adenoidectomy, or family history of hypoacusia.

Physical examination: measurement of height and weight. Microotoscopy in order to evaluate the external auditory canal and the eardrum was carried out blind, by two experienced ENT specialists (JM, IA).

Standard pure-tone audiometry was performed on all participants, according to standardized audiometric methods (ISO 389), using a clinical audiometer (Amplaid$^{®}$ 311) at octave intervals from 250 to 8,000Hz. All hearing tests were carried out by the same trained audiologist in a soundproof booth, with background levels well-below the accepted standards. A 5dB machine error rate associated with audiogram measurement was taken into account.

Audiograms were categorised as normal if the air conduction (AC) thresholds were ≤ 20dB across the frequency range of 250 to 8,000Hz. However, if an apparent loss of only 5dB of hearing decline at only one frequency was observed, the audiometry was also considered normal for the purposes of this analysis. Hearing loss (HL) was defined when AC thresholds were higher than 20 dB at one or more frequencies in the range of 250 to 8000 Hz. Bone conduction was performed in order to classify the type HL:

- **Conductive hearing loss** (CHL) was defined when AC thresholds were higher than 20dB with an air-bone gap (ABG) of at least 10dB at one or more frequencies, with bone conduction (BC) thresholds being less than 20dB at any frequency.

- **Sensorineural hearing loss** (SNHL) was defined when patients presented with AC thresholds lower than 20dB HL at one or more frequencies in the range of 250 to 8000Hz, with ABG lower than 10dB.

- **Mixed hearing loss** (MHL), both conductive and sensorineural, was defined when BC thresholds were worse than 20dB HL at one or more frequencies with an ABG of at least 10dB at one or more frequencies [10].

The degree of HL was based on the assessment of pure-tone air conduction average at four frequencies (500, 1,000, 2,000 and 4,000Hz), following the schemes adapted from the European Working Group on the Genetics of Hearing Impairment [24]. Mild HL included pure-tone air conduction averages between 20dB and <40 dB; moderate, from 40dB to <70dB; severe, from 70 dB to<95dB; and profound, ≥95 dB [12].

HL was also assessed using the American Academy of Otolaryngology 1979 (AAO) equation. This equation is broadly used in occupational hearing decline and is obtained as follows: The average of 500, 1,000, 2,000 and 3,000Hz thresholds was calculated for each ear. 25dB were subtracted from the average and the result was multiplied by 1.5. This result gave the percentage of HL for the ear. To calculate the binaural score the following formula was applied:

% binaural score = [5 x (best ear score) + 1 x (worst ear score)]/6

Brain auditory evoked potentials (BAEP)

BAEP was performed on TS patients and OCH group. BAEP's results were compared to reference population data.

BAEP were registered using the two-canal recording function of a Medelec Synergy EP machine. The lower filter was of 100Hz, and the upper of 3,000Hz. The stimulus consisted of alternating clicks, presented monaurally, at a rhythm of 20 times per second. The medium response of 1,500 stimulus was registered for 10ms. First of all, the latency of V wave was recorded at different stimulus intensities, between 30dB and a maximum of 110dB, in order to find out the hearing threshold and to establish the type of HL with the best accuracy. Auditory brain response (ABR) was carried out afterwards. The intensity of the applied stimulus was 60dB higher than the hearing threshold. Morphology, latencies of peaks I, III and V, as well as interpeaks I-III, III-V and I-V were also recorded. Two replications, each of 1,500 stimulus, were obtained for each stimulus intensity and for each tested ear. Each recording was individually analyzed by the testing audiologist and by two of the authors (AT, JS).

BAEP have been extensively validated as an objective diagnostic tool for SNHL, monitoring the pathway from the cochlea to the level of brainstem. Wave I is the result of the volley generated by the click stimulus in the distal part of the eighth cranial nerve. Consequently, changes in the amplitude or latency of this wave suggest damage to the cochlea or the distal part of the eighth cranial nerve. Nevertheless, abnormal absolute latencies of waves II-V or interlatencies I-III, III-V are strongly indicative of

retrococlear HL [25,26]. In CHL the hearing threshold is high, wave I to V are usually shifted to the right, the I-V interval is normal, and the latency-intensity curve for wave V runs above and parallel to the normal curve. However, in SNHL the hearing threshold may be high, the latency-intensity curve is of recruiting type so, at high intensity, the curve is normal but, at lower intensity, the wave V latency is disproportionately prolonged. Latencies in cases with SNHL are within the ranges of normal hearing individuals.

2.3. Statistical analysis

Data analysis was performed using the the software SPSS v19 (SPSS 19.0, SPSS Inc. Headquarters, 223 South Wacker Drive, Chicago, IL 60606, USA). Qualitative variables were described using frequency tables, whereas quantitative variables were described by their mean and standard deviation. A student T-test was performed to compare means between groups in those variables following normality criteria, according to Kolmogorov-Smirnov. Conversely, when the variables did not fit into normality criteria, a Mann Whitney U-test was carried out. A binomial test was used to compare frequency variables. A multiple regression analysis was carried out to asses the importance of several parameters in HL outcomes among TS patients. All statistical hypotheses were tested while considering an alpha error of 5% ($p < 0.05$).

3. RESULTS

Clinical and anthropometrical characteristics of the subjects are shown in Table 1. TS patients were shorter than OCH and controls. More than one third of TS patients had undergone tonsillectomy and/or adenoidectomy, while three quarters suffered from recurrent otitis media in childhood. These percentages are significantly higher in TS patients than controls. A low percentage of TS women had deformed external acoustic meatus or affected eardrum (Table 1).

Analysing pure-tone audiometry results, 27 (87%) of TS patients suffered from some degree of HL, compared with only 3 (20%) OCH and 11 (27%) controls. When outcomes of the AAO equation were compared between groups, TS women revealed significant HL in respect to OCH group and control group (Figure 1). More HL was found in TS patients compared to controls when considering the right ear (p=0.001), left ear (p<0.001) and binaural loss (p<0.001); and compared to OCH in right ear (p=0.015), left ear (p=0.02) and binaural loss (p=0.009). Additionally, AC thresholds in both right and left ears were higher in TS patients in frequencies from 1,000Hz to 8,000Hz, compared to OCH (p<0.05) (Figure 2). Similar results were found between TS and controls (p<0.01). No differences were found between right and left ears.

Following the classification criteria described previously, SNHL was the most frequent type of hypoacusia found in TS group [11 (35%) patients in the right ear and 13 (42%) in the left ear], followed by CHL [8 (26%) patients in the right ear and 8 (26%) more in

the left ear] and MHL [4 (13%) affected right ears and 4 (13%) left ears]. The low

percentage of affected controls was diagnosed by CHL [3 (7%) in the right ear and 7

(17%) in the left ear]. Conversely, few OCH suffered SNHL [2 (13%) in the right ear

and 3 (20%) in the left ear] or CHL [1 (7%) in the right ear and 1 (7%) in the left ear]

(Figure 3).

Patients were also differentiated according to the degree of HL (Figure 4). The majority

of patients of the control group and OCH presented normal hearing function, with a low

proportion of females with mild hypoacusia. Conversely, more TS patients suffering

moderate, severe or profound hypoacusia were found compared to controls and OCH.

Hearing threshold of the latency-intensity curve for wave V was higher in 19 (61%) TS

patients (14 bilateral and 5 unilateral), leading to the conclusion that hearing threshold

was higher in 33 ears (54.1%). However, only 20% (6 affected ears) of OCH patients

presented HL according to pure-tone audiometry results, and up to 8 TS patients with

impaired audiometry results presented normal BAEP. Analysing BAEP results and

following the classification criteria described previously, mild HL was detected in 18

ears (29.5%), moderated HL in 12 ears (19.7%), severe HL in 2 ears (3.3%), and

profound HL in only one ear (1.6%). CHL was present in 4 ears (6.5%), MHL in 3 ears

(4.9%) and SNHL in 26 ears (42.6%). Overall, type of HL evaluated by BAEP was in

accordance with audiograms, except in a group of TS patients analysed as mild CHL in

the audiometry, which was evaluated as normal in BAEP.

Finally, the results of BAEP were analysed. ABR-wave I was reliably indentified in 27 cases, wave III in 29, and wave V in all 31 TS cases. No significant differences on latencies, amplitudes, and interpeaks of waves I, III and V were found between TS and OCH, or TS and reference population [25] (Table 2).

3.1. Turner's syndrome sub-analysis

Several sub-analyses between groups of TS patients were performed in order to explore possible associations of HL with karyotype, hormonal status, history of recurrent otitis media and age.

Karyotype. TS patients were differentiated according to the presence of the short arm of X chromosome. Complete absence sub-group included patients with pure monosomy (45X0) or isochromosome (45X0/46i(X)). Remaining mosaicisms or structural anomalies formed the second sub-group. Significant differences were found between groups in 8,000Hz, where monosomies and isochromosomes presented a higher hearing threshold than the second sub-group (p=0.01 in Student T-test).

Hormonal status. The second sub-analysis differentiated TS patients according to hormonal status during puberty. Patients with normal puberty and women with TS without normal oestrogen levels at the end of the puberty were compared. No statistically significant differences were found between groups. Additionally, no differences were observed between TS patients who received GH during infancy and those who did not.

Age. Two groups of TS females were analysed according to age: from 20 to 35 and from 35 to 50 years. As expected, higher hearing thresholds in mid and high frequencies (2,000, 4,000 and 8,000Hz) were found in the oldest group ($p<0.05$).

History of otitis media. HL was higher among TS patients with recurrent otitis during childhood at 250, 500, 4,000 and 8,000Hz ($p<0.05$) (Figure 5). In a multiple regression analysis, which included all above-mentioned parameters as variables, history of recurrent otitis was the most weighted.

4. DISCUSSION

The main findings of the present study were: 1) more than a half of TS females presented with HL in pure-tone audiometry, as confirmed by BAEP; 2) SNHL is the most frequent type of hearing impairment among middle-aged women with TS; and 3) old age, altered karyotype and history of recurrent otitis may be predisposition factors to produce HL among TS patients.

In the present study, we observed HL as evaluated by audiometry in almost 90% of females with TS. Nevertheless, hearing dysfunction analyzed by BAEP was found in approximately one-half of TS patients. This concurs with previous studies [0,12]. These differences may be due to an upper normality threshold in BAEP (30dB *vs* 20dB in audiometry) and the higher objectivity of this neurological technique. However, direct comparisons with other studies are difficult due to the disparities in how HL has been defined and categorized. Most studies have been performed in children with TS (0, 9,

10, 72), with a high percentage of them showing CHL. The etiology of high incidence of middle ear pathology, including otitis media, in TS subjects, is thought to be due to early defects in lymphatic channels and aberrant anatomic shaping of structures derived from the first and second brachial arches, thereby causing abnormally horizontal Eustachian tubes and palatal dysfunction [73]. In our study, 12 TS females presented pure or mixed CHL.

Otherwise, the incidence of SNHL increases with old age [9]. Taking into account that our study's TS patients were from 20 to 50 years of age, comparison should be done with other studies with an age-matched population. Hederstierna and colleagues [11] studied 30 TS women aged 40-67 years, with mild to moderate HL, with the objective of localizing the lesion responsible for the SNHL and assessing central auditory function. As previously mentioned, ABR-latencies in the present study were within reference range in all 31 TS cases. In accordance with Hedestierna's study [11], ABR amplitudes and absolute and interpeak latencies of our TS cases were not significantly prolonged compared to the reference population. Up to 50% of TS cases had mild to moderate HL, and three of them (10%) showed an absence of wave I, suggesting a cochlear dysfunction as the cause of their hearing impairment. Unlike Hedesternia's results, shorter V latencies were not found in our study. Previous studies [0,73] also showed prolonged absolute ABR latencies, but interpeak latencies were completely normal in all cases.

The most frequent type of HL found in our population was SNHL. The literature characterizes the SNHL in TS women according to two different patterns: a bilateral symmetrical mid-frequency dip (maximal at 2,000 Hz) [29, 30] and a high-frequency down-sloping SNHL [8,30]. No cases of clear mid-frequency dip were found in our TS females and this could be due to the fact that most of TS women develop a moderate to profound high-frequency HL [11], leaving only the low-frequencies available. This audiometric pattern was the most frequently observed in our TS population.

A cell cycle delay has been explained as a possible cause of SNHL in TS. Whereas in healthy subjects the density of hair cells in the Organ of Corti is highest in the middle turn of the cochlea, a lack of sensory hair cells within the cochlea exists in TS patients. This defect has been hypothesized as the cause of the mid-frequency HL, while the apoptosis attributable to age has been suggested as responsible for presbyacusia [74]. Therefore, both CHL and SNHL could be explained by developmental alterations in TS women [0]. The severity of TS dysmorphology is related to karyotype [1, 15, 75]. Some findings suggest that the genes responsible for hearing impairment may be located on the short arm of the X-chromosome [7]. According to this hypothesis, a higher frequency of ear and hearing defects was expected in TS patients with monosomy or isochromosome compared to those with a mosaicism or structural anomaly [10]. The results of the sub-analysis perfomed in our study between monosomy or isochromosome

and other karyotypes were in accordance with this hypothesis, showing worse results in high frequencies.

Additionally, the lack of endogenous oestrogens has been proposed as a contributing cause for SNHL. Oestrogen receptors have been found in the inner ear of both animals 18] and humans [77]. Coleman and colleagues proved improvement of BAEP latency scores in ovariectomised rats after hormonal replacement therapy [78]. A lack of appropriate hormonal treatment during childhood has been suggested as one cause of the extensive hearing problems found among older TS women [14, 72]. This would suggest that no statistically significant differences in hearing status were found between TS with normal hormonal status at 16 years of age, or TS females with a lack of sexual development. Furthermore, it is worth noting that no significant differences were found between controls and OCH in any form of hearing test, while differences were found between OCH and TS patients. TS is a suitable human model for the assessment of physiological processes in organs that have matured in a deficient oestrogen environment [11], as are indeed patients with congenital hypogonadisms having normal karyotype. No hearing decline was found among OCH patients, which additionally suffered an even greater delay than TS in the oestrogen deficiency diagnosis due to the lack of dysmorphology (Table 1). This new study group suggests oestrogens have a minor role in HL, although further studies are needed to confirm or discount this.

GH, which has been recommended since 1990 to treat the short stature which characterizes TS females, has been related with the etiology of TS hearing impairment [12]. However, some studies concluded that GH has no impact on HL either in children [13] or in adult females with TS [72]. Accordingly, this study rules out that GH therapy has a significant impact on hearing function among adult TS women.

Hearing decline in women is in general fairly slow up until the age of around 50 years, but this accelerates after the menopause [6]. TS patients suffer a rapidly progressive hearing decline with age. The rate of progression in young and middle-aged women with TS is on a level comparable to that seen in 70-89 year-old women in the general population, especially in high frequencies. As regards age, higher hearing threshold values were observed in the oldest group in mid and high frequencies, and this concurs with previous studies [6, 7, 12]. This decline in hearing may reflect a premature loss of sensory function, residual cochlear sequelae of otitis media, or both [7]. It is important to note that the hearing impairment becomes more of a social handicap when a high-frequency loss combines with the mid-frequency dip developed previously [6].

Interestingly, worse results in the lowest and the highest frequencies were found between TS patients with and without history of otitis media during childhood. Mid-frequency dip pattern seems to be independent of otitis media and it is typically present in TS adolescents [0, 10]. No differences were found between groups at mid-

frequencies, probably due to alterations of these frequencies in a high percentage of TS adolescents, with and without a history of middle ear infection.

Some limitations exist in the present study. The low sample size, especially in the case of TS sub-groups analyses, leads to a cautious interpretation of these results. Congenital hypogonadisms are rare diseases around the world. Therefore, large series are difficult to obtain. However, some selection biases have been avoided with the recruitment through a gynaecological unit instead of special otorhinological referral clinics, thereby providing the study with a more realistical prevalence of hearing disorders in TS women. In addition, the comparison between TS and OCH provides us with a completely new type of data for the study of the role of oestrogens in hearing function. This study is intended to stimulate future, larger scale, adequately powered, and better still, multicentre trials to address this issue. This will in turn provide a larger basis for eventual metaanalysis to help clarify the value of this approach.

In conclusion, a progressive HL is associated with TS, with SNHL being the most frequent pattern of hearing decline. The etiology of HL is without doubt heterogeneous, with a strong genetic influence, and a recurrent history of otitis media. However, the role of the lack of endogenous oestrogens becomes less important, although further studies are needed to substantiate this fact more firmly. Regular audiometric test in adults patients with TS are required because of their much earlier development of presbyacusia combined with lower percentages of complaints about subjective hearing

deterioration. However, medical intervention to reduce HL in women with TS should be restricted to otitis media prevention.

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TABLE 1. Clinical and anthropometrical characteristics of the three study groups. Comparisons between groups were performed using student T-test for continuous variables, while a binomial test was used to compare percentages. BMI = Body Mass Index. HRT = Hormone Replacement Treatment.

	Controls (n = 41)	Other congenital hypogonadisms (n = 15)	Turner's syndrome (n = 31)
Age, years (mean ± SD)	34.6 ± 7.6	32.7 ± 8.5	36.6 ± 8.1
Height, cm (mean ± SD)	163.4 ± 5.2	162.1 ± 8.7	148.8 ± 7.5[a]
BMI, kg/m^2 (mean ± SD)	22.7 ± 4.0	22.3 ± 13.8	25.1 ± 3.8[b]
Age at diagnosis, years (mean ± SD)	-	16.7 ± 3.0	10.5 ± 10.2[c]
Age at beginning of HRT, years (mean ± SD)	-	17.8 ± 3.7	17.8 ± 5.3
Spontaneous menarque, N (%)	41 (100)	9 (60)[a]	10 (32)[b]
Hearing history			
Familial hipoacusia history, N (%)	6 (15)	3 (20)	5 (16)
Adenoidectomy, N (%)	4 (10)	1 (6)	10 (32)[b]
Tonsilectomy, N (%)	4 (10)	1 (6)	11 (35)[b]
Recurrent otitis media, N (%)			
No	13 (87)	13 (87)	8 (26)[b]
Bilateral	2 (13)	2 (13)	12 (39)
Only right	0 (0)	0 (0)	5 (16)
Only left	0 (0)	0 (0)	6 (19)
Deformed external acoustic meatus, N (%)			
No	15 (100)	15 (100)	27 (87)
Bilateral	0 (0)	0 (0)	3 (10)
Only right	0 (0)	0 (0)	0 (0)
Only left	0 (0)	0 (0)	1 (3)
Affected eardrum, N (%)			
No	15 (100)	15 (100)	24 (77)
Bilateral	0 (0)	0 (0)	3 (10)
Only right	0 (0)	0 (0)	1 (3)
Only left	0 (0)	0 (0)	3 (10)

[a] p <0.01 and [b] p<0.05 comparing with control group

[c] p <0.05 comparing with other congenital hypogonadisms.

SD, standard deviation

TABLE 2. Results of Brain Auditory Evoked Potentials (BAEP) of patients with Turner's syndrome and other congenital hypogonadisms. Values of the reference Spanish population are shown. No statistically significant differences were found between groups using an ANOVA test.

BAEP values (Mean ± SD)	Reference population	Other congenital hypogonadisms (n = 15)	Turner's syndrome (n = 31)
Audiometric hearing threshold (dB)	< 20	23.37 ± 8.48	36.00 ± 18.17
BAEP hearing threshold (dB)	< 30	31.99 ± 10.40	48.24 ± 20.69
Latency Wave I (ms)	1.7 ± 0.15	1.62 ± 0.31	1.80 ± 0.23
Latency Wave III (ms)	3.9 ± 0.19	3.67 ± 0.74	3.86 ± 0.18
Latency Wave V (ms)	5.7 ± 0.25	5.43 ± 1.10	5.75 ± 0.30
Amplitude Wave I (µV)	0.28 ± 0.14	0.35 ± 0.16	0.19 ± 0.10
Amplitude Wave III (µV)	0.23 ± 0.12	0.31 ± 0.14	0.22 ± 0.10
Amplitude Wave V (µV)	0.43 ± 0.16	1.44 ± 5.01	0.35 ± 0.14
Interpeak I-III (ms)	2.1 ± 0.15	1.98 ± 0.57	2.05 ± 0.18
Interpeak III-V (ms)	1.9 ± 0.18	1.68 ± 0.51	1.85 ± 0.17
Interpeak I-V (ms)	4.0 ± 0.23	3.66 ± 1.07	3.89 ± 0.25

FIGURES
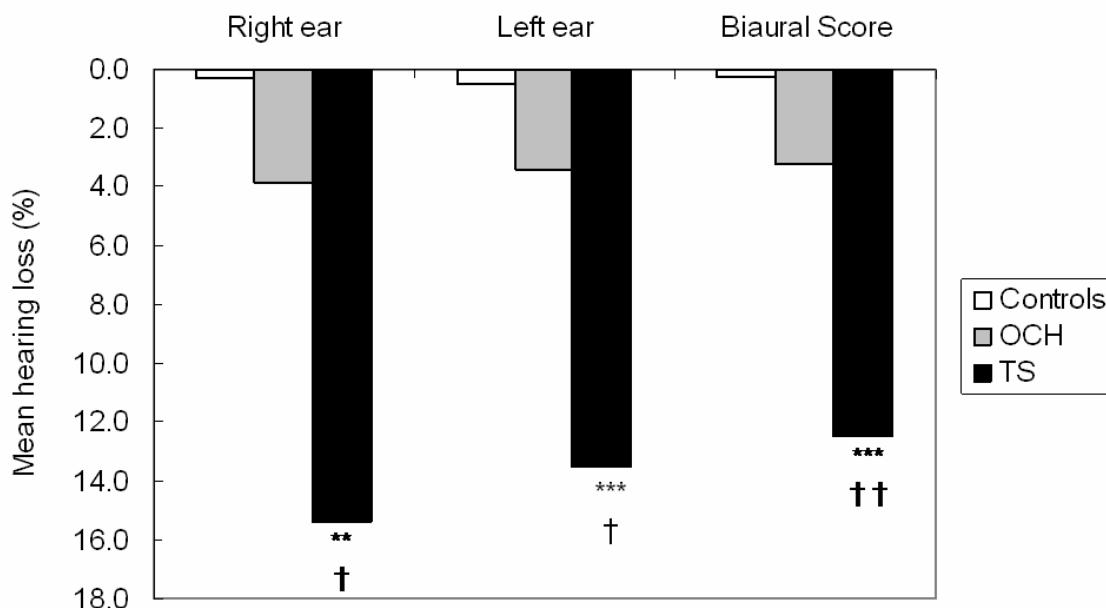
Figure 1. Percentage of hearing loss according to the equation of the American Academy of Otolaringology (AAO). Mann-Whitney Test was performed to compare percentage of hearing loss between groups.

[**] p <0.01 comparing Turner's syndrome group (TS) with controls

[***] p <0.001 comparing TS with controls

[†] p <0.05 comparing TS with other congential hypogonadisms (OCH)

[††] p <0.01 comparing TS with OCH
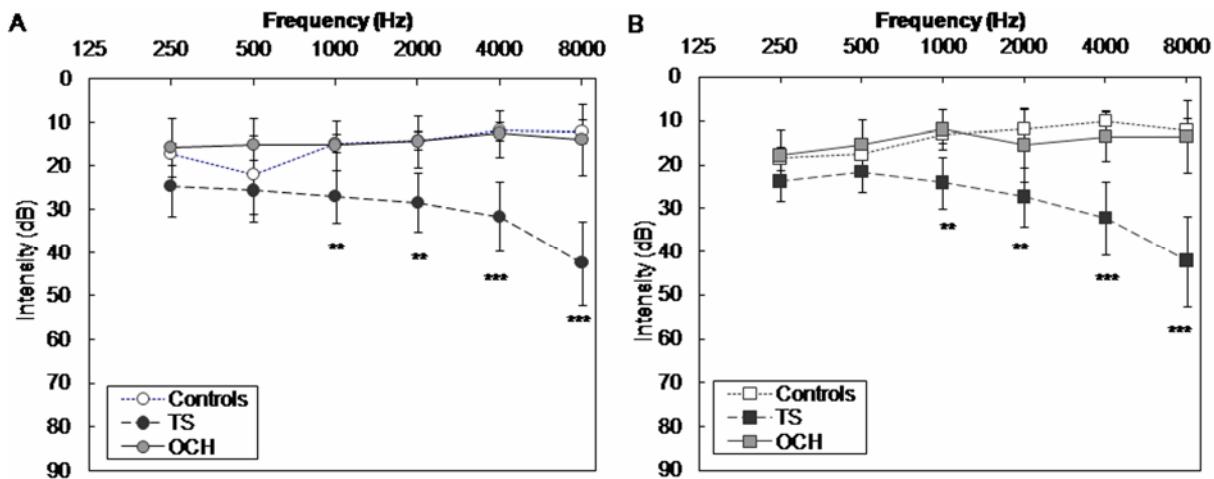
Figure 2. Pure-tone audiometry results of the three study groups. (A) Right ear and (B) left ear. Air conduction hearing thresholds across the frequency range from 250 to 8,000Hz. Average and confidence interval 95% are depicted. **, p<0.01 and ***, p<0.001 comparing TS (Turner's syndrome group) with control group. No statistically significant differences were found between TS and OCH (other congenital hypogonadisms).
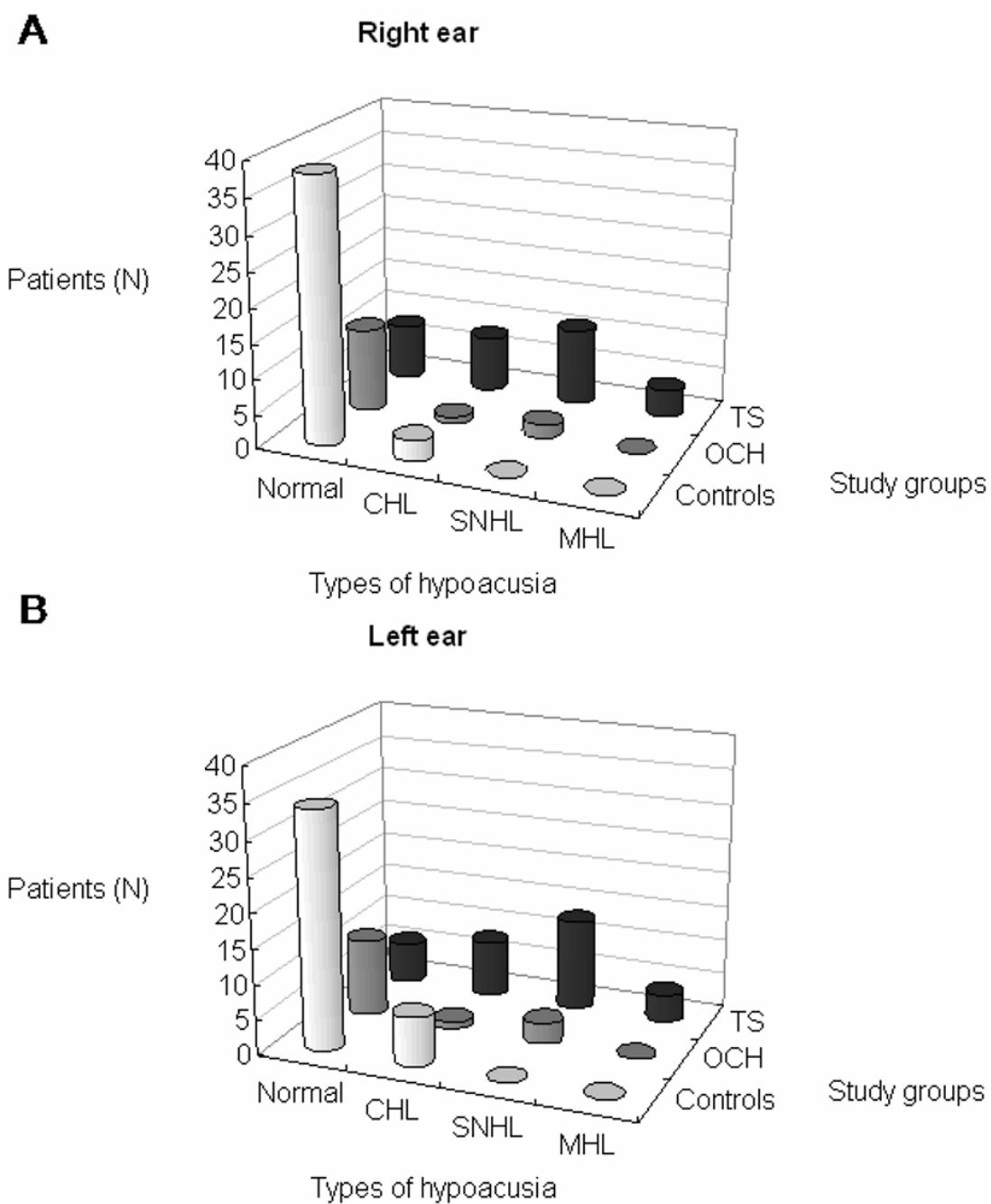
Figure 3. Number of patients in the three study groups and types of hypoacusia. CHL:

conductive hearing loss; SNHL: sensorineural hearing loss; MHL: mixed hearing loss;

TS: Turner's syndrome; OCH: other congenital hypogonadims.
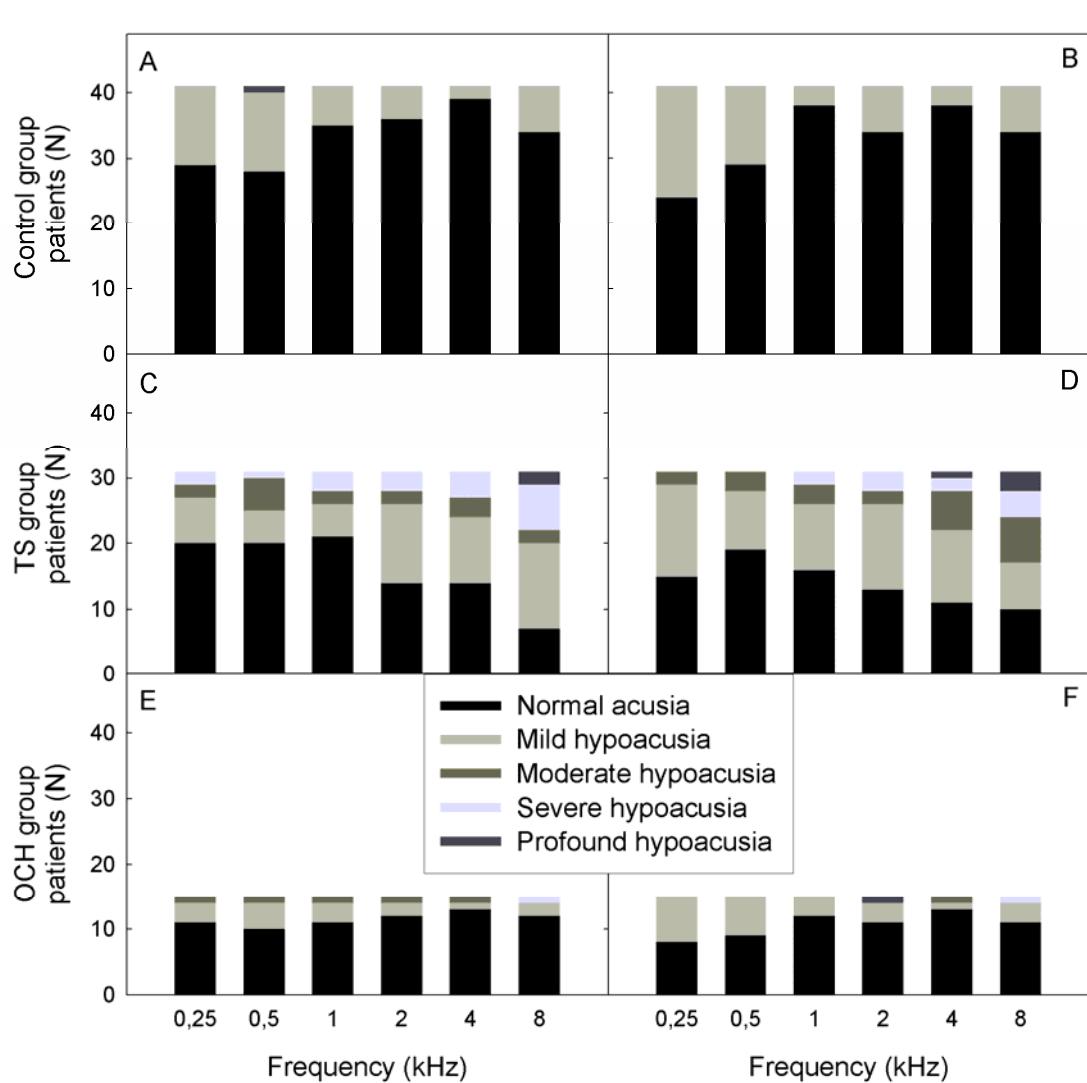
Figure 4. Number of patients in the three study groups and degrees of hypoacusia. (A. and B) control groups, (C and D) Turner's syndrome patients (TS), (E and F) Other congenital hypogonadims (OCH). A, C and E depict right ears and B, D and F depict left ears.
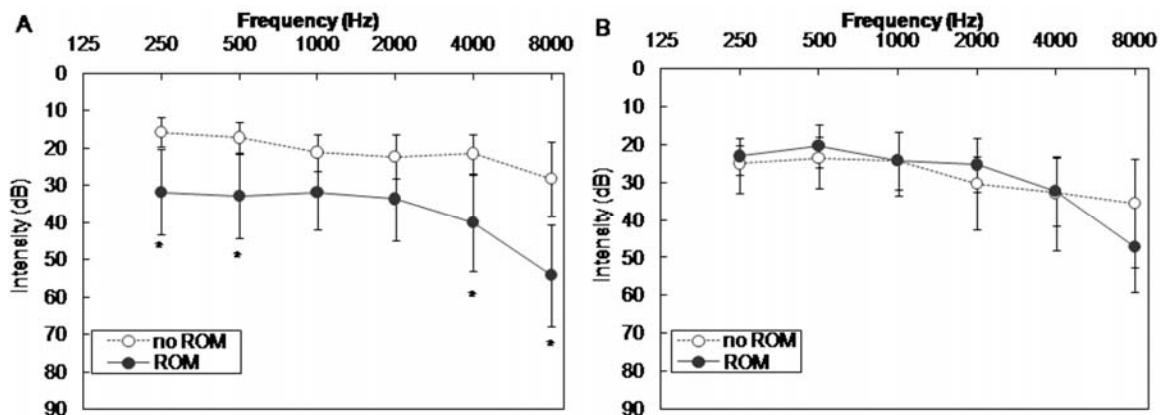
Figure 5. Comparative analysis of audiometry outcomes (air conduction hearing thresholds) between Turner's syndrome (TS) patients with and without history of recurrent otitis media (ROM). (A) Right ear and (B) left ear. Average and 95% confidence interval are depicted. *p<0.05 between ROM and no ROM TS subgroups.

4. LOSS OF SMELL BUT NOT TASTE IN ADULT WOMEN WITH TURNER'S SYNDROME AND OTHER CONGENITAL HYPOGONADISMS.

Article publicat a **Maturitas.**

Loss of smell but not taste in adult women with Turner's syndrome and other congenital hypogonadisms.

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Loss of smell but not taste in adult women with Turner's syndrome and other congenital hypogonadisms

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ABSTRACT

Objectives: To assess the impact of Turner's syndrome (TS) and other congenital hypogonadisms (OCH) on the sense of smell and taste.

Design: An analytical study of three independent cohorts was designed: patients affected by TS, OCH, and a control group of healthy women taking contraception.

Setting: Gynaecological Endocrinology Unit and Smell Clinic in Rhinology Unit of Hospital Clinic of Barcelona.

Participants: Thirty TS patients between 20 and 50 years of age receiving hormone replacement treatment (HT) were included as the exposed cohort; fourteen age-matched women with OCH taking HT were recruited; forty-three age-matched healthy controls receiving hormone contraception treatment were selected as the control group. This group was matched with an historical cohort of forty healthy women without contraception, used to validate BAST-24 in Hospital Clinic of Barcelona.

Interventions: Clinical history, presence of nasal symptoms, general physical examination, nasal endoscopy, and Barcelona Smell Test-24 (BAST-24) and gustometry were carried out on all patients.

Main measures: TS physical dysmorphology features, intensity of nasal symptoms and signs of nasal obstruction were collected. BAST-24 test included 24 odours to assess both sensory (detection, memory and forced choice) and sensitivity (intensity, irritability, freshness and pleasantness) odour characteristics, as well as 4 tastes to evaluate taste domains (detection and forced choice).

Results: Healthy women taking hormone contraception felt odours with more intensity ($p = 0.002$) and less irritability ($p < 0.001$) than the historical cohort. TS patients showed a significant impairment in smell memory ($p < 0.005$) and forced-choice ($p < 0.001$) compared with controls taking contraception, whereas no differences were found in odour sensitivity. Detection of taste was successful in 100% of patients. When considering only individual tastes, none of them showed statistically significant differences between groups.

Conclusion: Patients with TS show the impairment of smell but not of taste, compared to OCH and healthy controls taking contraception. Smell sensitivity was not affected.

1. Introduction

Disorders in olfactory function are common in the general population, frequently associated with chronic sinusitis and nasal polyposis, traumatic brain injury, upper respiratory tract infection or allergic rhinitis [1,2]. However, more than 200 conditions have been related with changes in olfaction, such as neurodegenerative disorders, chemical toxic agents or congenital diseases. As Kallmann syndrome, Turner's syndrome (TS) has been associated in medical literature with disordered olfactory and taste function [3]. Unfortunately, this association is based on anecdotal observations, and the mechanisms responsible for the loss of smell are poorly understood.

TS is a human genetic disorder affecting females, characterized by the absence of all or part of one X chromosome. It is the most common chromosomal disorder among women, with a prevalence of up to 1/2500 in living females [4,5]. The most important features of TS are short height and gonadal dysgenesis. In most cases, this condition leads to oestrogen insufficiency, with delayed puberty and primary amenorrhoea. Heart and kidney congenital malformations are associated, as well as several physical dysmorphology

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[6,7]. Increased morbidity with a number of medical conditions, such as osteoporosis, hypothyroidism, diabetes, dyslipemia, hearing loss or non congenital cardiac or nephro-urological changes, has been documented. Therefore, follow-up in specific gynaecological and endocrinological units is recommended with co-ordination between different specialities [7–10].

Considering smell and taste dysfunctions, only two studies have been published on TS patients. Nine TS women were found to have elevated detection and recognition thresholds to three odourants assessed, as well as sour and bitter thresholds using a taste test [11]. Valkov published similar findings in 20 patients with TS eight years later [12]. Some authors have reported that olfactory detection is higher in females than in males [13,14], although the explanation for these gender differences is not yet clear. The nature of odour identification, closely related to cultural items, usually limits the use of olfactory tests to the country or region where they have been developed and validated. Therefore, different odour-identification tests for clinical use have been developed in different countries [16,15–18]. Cardesín et al. [19] validated the Barcelona Smell Test 24 (BAST-24) as a reliable method to assess olfactory function in clinical practice for the Spanish and Mediterranean population.

The aim of this project was to analyse the type and prevalence of smell and taste abnormalities in adult patients with TS. Symptoms, physical and nasal examination, and olfactometry–gustometry by the BAST-24 were used for this purpose. Remarkably, to the best of our knowledge, no previous studies where TS women were compared with patients with other congenital hypogonadisms (OCH) in terms of smell and taste do exist. On the above evidence, the current investigation was undertaken to deal with this subject using TS patients, but also three appropriate comparator groups: OCH, a reference control group taking exogenous hormones, and an historical cohort of age-matched women not receiving hormones [19].

2. Materials and methods

2.1. Study design and population

An analytical study of three independent cohorts was designed. One cohort corresponds to TS patients recruited at the Gynaecological Endocrinology Unit of the Hospital Clinic of Barcelona. The diagnosis of TS was confirmed by blood karyotype showing total or partial absence of X chromosome, or other X abnormalities, in at least, more than 10% of read cells. Inclusion criteria were TS subjects between 20 and 50 years of age receiving hormone replacement treatment.

A second cohort was composed by women with OCH and wild-type karyotype. From this group, Kallman's syndrome patients were excluded due to the well-known absence of the smell sense. All of them were also receiving hormone replacement treatment due to their congenital hypoestrogenism.

The third cohort included non-exposed age-matched cases, as the study's control group, who were all treated with oestrogen and progestagens with the aim of contraception. They were recruited by the gynaecological department, none of them taking any other drug that may alter the study results.

Additionally, the sense of smell of the third cohort was compared with an historical cohort from 120 healthy volunteers without subjective olfactory disturbances, used for the validation of BAST-24 test in Hospital Clinic of Barcelona [19]. Only females between 20 and 50 years of age were selected from the 120 volunteers to match characteristics of the study's group, in order to avoid possible bias.

Exclusion criteria for the exposed and healthy cohort were the presence of acute or chronic pathologies non-related with the syndrome being studied which could interfere with the analysis, such

as head injury, nasal polyps, exposure to toxics or severe asthma. The study was approved by the Ethics Committee of the Hospital Clinic of Barcelona and all patients were informed about the study and the interventions that would be performed. Signed informed consent was obtained from all patients at the time of inclusion.

2.2. Interventions

Clinical history and physical examination: Ages at diagnosis of hypogonadism, spontaneous menarche or primary amenorrhoea, diagnosis of cardiac or renal malformations were collected. Height, weight, description of phenotypic dysmorphology described in TS patients (epicanthus, ocular ptosis, strabismus, deformity in the pinna, micrognathia, cleft palate, short neck, pterygium colli, limbs lymphedema, cubitus valgus, genu valgum, low-set ears or low hair implantation, syndromic facies) were examined.

Nasal symptoms: The intensity of nasal obstruction, rhinorrhoea, nasal itching, sneezing, loss of smell, and facial pain were scored on a visual analogical scale (VAS). Score was performed on a 10 cm line where patients had to cross with a short perpendicular line from 0 (no symptom) to 10 (the most severe symptom).

Nasal endoscopy: A rigid endoscope (2.8 mm diameter and 30° angle) was used to examine the nasal cavities to evaluate nasal mucosa, septum deviation, turbinate and adenoid hypertrophy, and chronic rhinosinusitis with or without nasal polyps.

2.2.1. BAST-24 test – olfactometry

As previously described [19], 24 odours were used in the BAST-24: (a) 20 odours to assess the 1st cranial nerve (olfactory): banana, gasoline, lemon, rose, onion, smoked, anis, coconut, vanilla, melon, mandarin, bitter almond, pineapple, cheese, strawberry, mushroom, eucalyptol, clove, turpentine, and peach; and (b) 4 odours to asses the 5th cranial nerve (trigeminal): formaldehyde, vinegar, ammonia, and mustard. After being exposed for 5 s to an odourant, patients were asked to answer three questions for smell sensory domains: (1) to test smell detection: "Did you smell any odour?"; (2) to test smell recognition/memory: "Did you recognize this odour?"; and (3) to test smell forced-choice: "Which of these four odours did you smell?".

For smell sensitivity domains, four more questions were asked: (1) to test smell intensity: "Was the odour intense?"; (2) to test smell irritability: "Did you find the odour irritable, causing nasal itching or tearing?"; (3) to test smell freshness: "Did you find the same odour refreshing?"; and (4) to test smell pleasure: "Did you like this odour?". Answers to these questions were "yes/no".

2.2.2. Gustometry

Four powdered tastes were used for the gustometry test: sweet, salty, sour and bitter. After leaving with a hyssop a small quantity of each powder on the tongue, patients spread the powder all over the mouth for 5 s to detect the taste. Patients were asked two questions by the researcher: (1) to test taste detection: "Did you taste any substance?"; and (2) to test taste forced-choice: "How did the powder taste: sweet, salty, sour or bitter?"

2.2.3. Statistical analysis

Qualitative variables were described using frequency tables, whereas quantitative variables were described by their average and standard deviation. An unpaired Student's *t*-test was performed to compare quantitative variables, whereas a binomial test was undertaken to compare qualitative variables. To analyse the possible differences in BAST-24 and gustometry outcomes, a Kruskall–Wallis test was performed. In those cases showing significant difference, a *U*–Mann–Whitney test was carried out to know between which groups these differences existed. All statistical hypotheses to be tested were carried out considering an alpha

Table 1
Clinical characteristics of the three groups of women included in the present study: Turner's syndrome (TS) hypogonadism, other congenital hypogonadism (OCH) and the control group (age-matched healthy women taking hormone contraception). For comparison of categorical and numerical variables Fisher's exact test and Student's t-test were used respectively.

	Control group, n = 43	OCH, n = 14	TS, n = 30	p
Age (mean ± SD)	34.8 ± 7.5	33.5 ± 8.3	36.7 ± 8.2	NS
Smoker, N (%)	6 (14)	3 (21)	3 (10)	NS
Allergic rhinitis, N (%)	17 (40)	5 (36)	12 (40)	NS
Asthma, N (%)	8 (19)	1 (7)	1 (3)	NS
Hypertrophic turbinates, N (%)	10 (23)	3 (21)	7(23)	NS
CRS/Nasal polyps, N (%)	0 (0)	0 (0)	0 (0)	NS
Deviated nasal septum, N (%)	18 (42)	3 (21)	15 (50)	NS
Cleft palate, N (%)	1 (2)	1 (7)	4 (13)	NS

NS, non significance between the three groups; SD, standard deviation; CRS, chronic rhinosinusitis.

error of 5%, and using the software SPSS v19 (SPSS 19.0, SPSS Inc. Headquarters, 223 South Wacker Drive, Chicago, IL 60606, USA).

3. Results

Thirty patients aged between 20 and 50 years, diagnosed with TS were included in the first cohort. In the second group, fourteen patients with OCH fulfilled the inclusion criteria: six patients with congenital hypergonadotrophic hyponadism, and eight patients with congenital hypogonadotrophic hypogonadism. The study's control group consisted of 43 age-matching healthy females receiving hormone contraception, and their olfactometry test was compared with an historical cohort of 40 healthy women from 120 volunteers used for the validation of BAST-24 test [19].

Clinical characteristics of the three groups designed for the current study are shown in Table 1. No differences related to rhinological history outcomes were found among the three groups of the study (Table 1). Using VAS to score nasal symptoms severity, no statistically significant differences between groups were found.

Given that TS and OCH were receiving hormone replacement treatment due to their congenital hypoestrogenism, the following statistical analysis was carried out when comparing hypogonadism patients to healthy women taking hormonal contraception. In order to validate our control group of women, a comparison was performed with a group of age-matched healthy women (n = 40). This data was extracted from the BAST-24 test validation [19]. No statistically significant differences were found among sensory smell domains (detection, memory and forced-choice) between groups (Fig. 1A). However, when considering parameters of smell sensitivity (intensity, irritability, freshness and pleasure), healthy women receiving hormone contraception treatment defined odours with more intensity and less irritability than healthy females not taking hormones.

TS patients showed a significant impairment in smell forced-choice compared with controls taking contraception (Fig. 2A). However, these differences were not found in women with OCH, compared with either these controls or TS patients. No differences on smell sensitivity characteristics were found between groups (Fig. 2B).

TS patients were studied according to their karyotypes (Table 2). The first group included pure monosomy patients (45X0), more frequently associated with major TS stigmata and congenital malformations. The second group included other karyotypes, such as mosaicism, isochromosomes, ring chromosomes, and X-deletions, in monosomy or mosaicism. No statistically significant differences were found in either sensorial or smell sensitivity outcomes between these two TS sub-groups.

When assessing the sense of taste, detection was reported by 100% of patients. Considering individual tastes, no patients showed statistically significant differences between groups. However, it is worth noting that 23% of TS patients wrongly identified the

sour taste, whereas only 5% of healthy controls taking contraception answered incorrectly as well (p = 0.083, Table 3). Furthermore, when the average percentage of correct answers (forced-choice) from each group was assessed, TS patients scored 91.7%, whereas the control group taking contraception scored 97.1% (p = 0.051, Table 3).

4. Discussion

The main findings of the present study were: (1) differences in smell sensitivity characteristics (intensity and irritability) in women receiving hormone contraception compared with healthy women not receiving exogenous hormones; (2) TS patients reported impairment in smell forced-choice compared with healthy controls taking contraception; and (3) the sense of taste was similar among the four different groups.

Considering the sensitivity characteristics of smell, women taking hormone contraception felt odours more intensely and less irritably than women not taking hormones. No differences in either sensitivity (freshness or pleasure) or sensory characteristics (detection, memory and forced-choice) were found. Some studies have reported that nasal physiology and smell sensitivity are influenced by the menstrual cycle phases, pregnancy or hormone contraceptives [3,20–22]. However, more recent publications could not find significant differences in olfactory function between women with different hormonal status [23–25]. The mechanisms by which sexual hormones influence the sense of smell are poorly understood. In accordance with a recent review [26], complex relations exist between the functional properties of the human olfactory system and neuroendocrine factors. Previous conclusions of simple intercourses between odour perception and reproductive hormones levels are oversimplifications of the possible influence of the endocrine system on smell function.

Table 2
Clinical characteristics related to karyotypes of Turner's syndrome patients. No differences between both sub-groups were found.

	Puremonosomykaryotype (45X0) (n = 10)	Other karyotypes[a] (n = 20)
Age, years (mean ± SD)	39.6 ± 6.0	35.2 ± 13.0
Height, cm (mean ± SD)	144.2 ± 4.5	150.8 ± 7.8
Age at diagnosis, years (mean ± SD)	6.0 ± 6.6	13.0 ± 11.2
Spontaneous menarque, N (%)	3 (30)	6 (30)
Minor Turner stigmata[b], N (%)	10 (100)	14 (70)
Major Turner stigmata[c], N (%)	4 (40)	5 (25)
Cardiac malformations, N (%)	5 (50)	1 (5)
Renal malformations, N (%)	1 (10)	5 (25)

[a] The group includes mosaicism, isochromosomes, ring chromosomes, and X-deletions, in monosomy or mosaicism.
[b] Short stature, cleft palate, genu valgum, low-set ears.
[c] Pterigium coli, short neck, short extremities, syndromic facies.
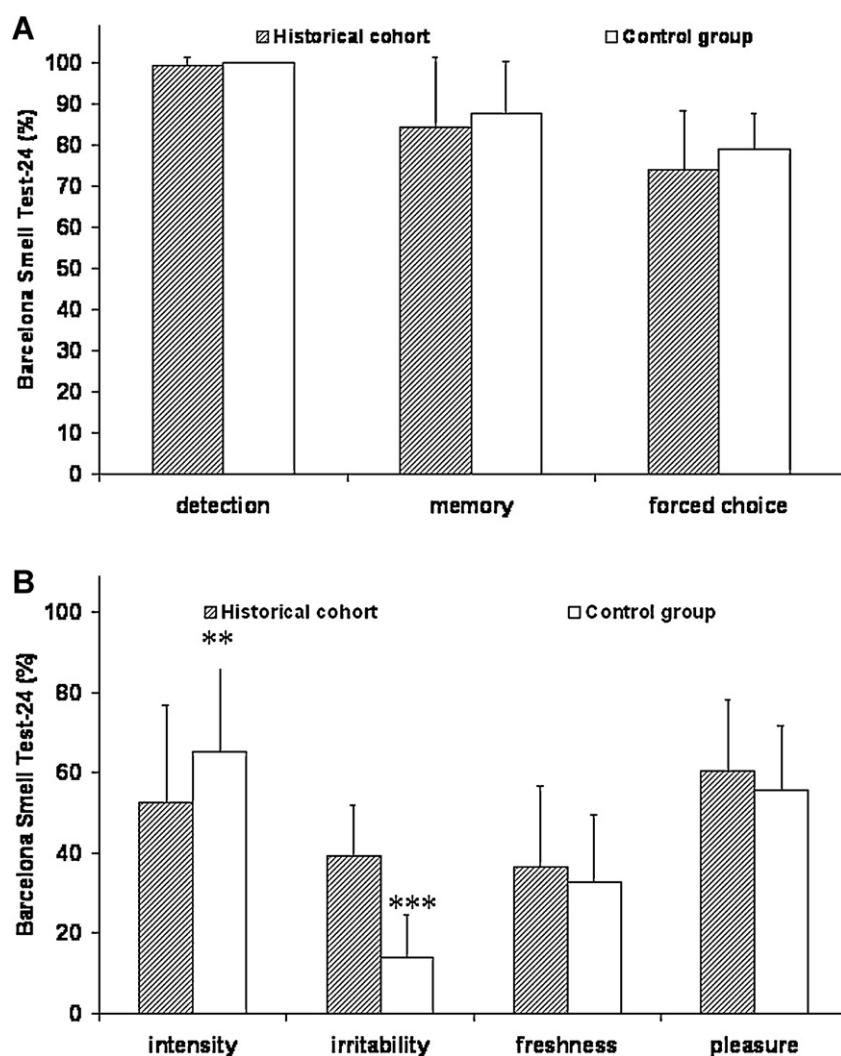
Fig. 1. Barcelona Smell Test (BAST-24) subjective olfatometry. Comparison between an historical cohort of age-matched healthy women (without hormonal contraception) and the study's control group (with hormonal contraception). (A) Sensorial smell domains, and (B) sensitive smell domains. Mann–Whitney U test (**$p < 0.01$; ***$p < 0.001$; compared to the historical cohort). Means and SD of the percentage of positive answers are depicted.

Significant differences were found between TS women and the healthy controls taking contraception in one sensory olfactory outcome: lower scores on smell forced-choice. However, no differences were observed between these healthy control group and OCH, suggesting a possible genetic cause instead of a hormonal reason, for this smell dysfunction. In addition, no differences among the groups were observed when the smell sensitivity characteristics such as intensity, irritability, freshness or pleasure, were analysed. To the author's knowledge, no previous studies have been published considering the sensitivity characteristics of smell patients with hypogonadisms.

Although the frequency of chemosensory disorders is closely related with the age of the subjects, the evidence of major olfactory impairment is over 80 years of age, while only a small percentage of people under the age of 65 evidence a decreased ability to detect and identify odours [15,27,28]. In our study, only patients between 20 and 50 years old were included; thereby, the sub-analysis of dividing groups according to age was not performed.

An oronasal examination was performed on all patients recruited for the study in order to diagnose inflammatory, neoplastic, traumatic or developmental alterations within the nasal cavity which could lead to olfactory dysfunction. It is well known that

Table 3

Gustometry. Individual and overall taste test of the three groups included in the present study: Turner's syndrome (TS) hypogonadism, other congenital hypogonadism (OCH) and the control group (age-matched healthy women taking hormone contraception).

Taste		Control group ($n = 43$)	OCH ($n = 14$)	TS ($n = 30$)
Individual taste	Salted, N (%)	42 (98%)	11 (78%)	29 (97%)
	Sweet, N (%)	42 (98%)	14 (100%)	29 (97%)
	Sour, N (%)	41 (95%)	13 (93%)	23 (77%)
	Bitter, N (%)	42 (98%)	13 (93%)	29 (97%)
Overall taste	Detection %	100%	100%	100%
	Forced choice, %	97.1%	91.1%	91.7%

TS, Turner's syndrome.
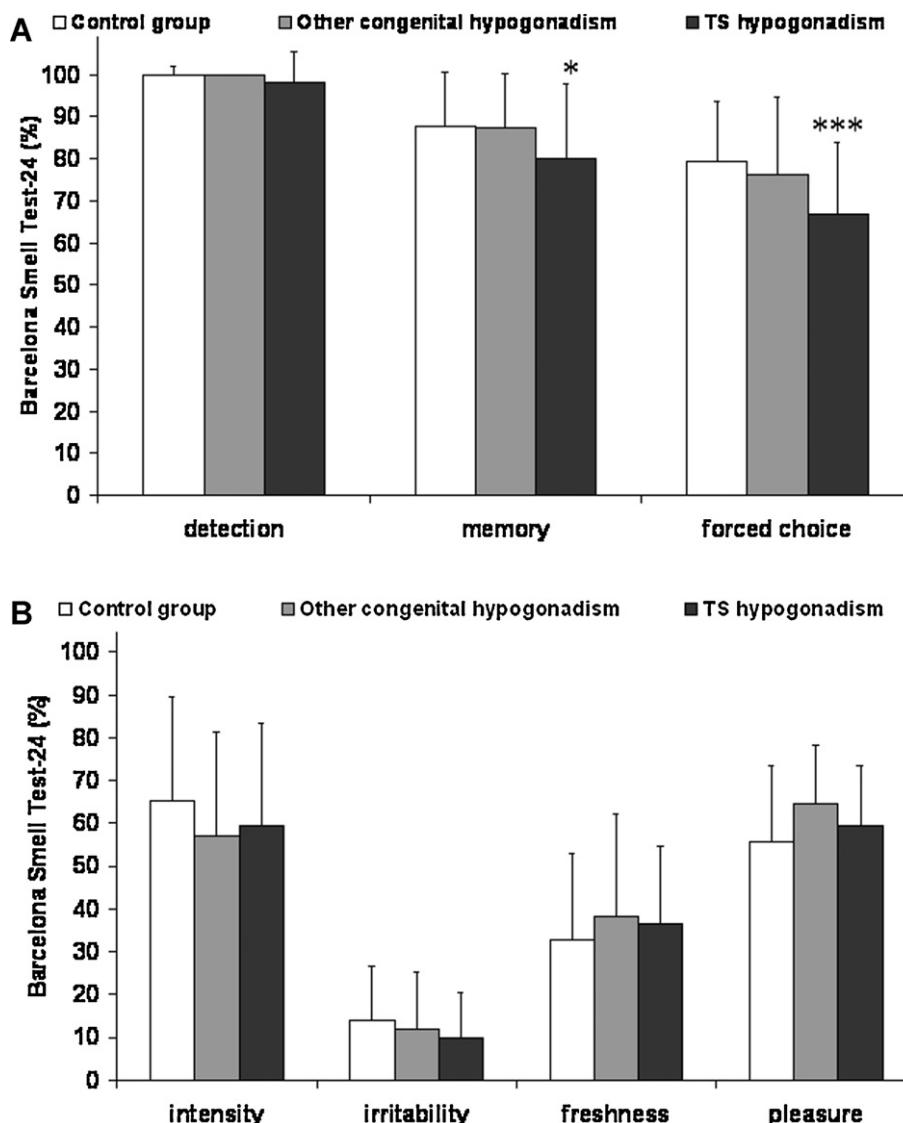
Fig. 2. Barcelona Smell Test (BAST-24) subjective olfactometry. Comparison between Turner's syndrome (TS) hypogonadism, other congenital hypogonadism (OCH), and the study's control group (with hormonal contraception). (A) Sensorial smell domains, and (B) sensitive smell domains. Mann–Whitney U test (***$p < 0.001$; compared to the control group). Means and SD of the percentage of positive answers are depicted.

upper respiratory infections such as the common cold can temporarily decrease or eliminate smell sense by blocking airflow to the olfactory receptor region, as well as allergic rhinitis [2,29]. The percentage of smokers and patients with allergic rhinitis or asthma was not statistically different among the groups of the study, and no differences were found in the variables of the oronasal physical examination among the three groups. Thereby, causes of nasal obstruction which could disturb the results of the olfactometry were not found among patients.

The first report which described abnormalities in olfaction among patients with gonadal dysgenesis was published in 1967 [11]. Detection and recognition thresholds for pyridine, thiophene and nitrobenzene vapours were determined in nine patients with chromatin negative gonadal dysgenesis. Nevertheless, Henkin's results are difficult to compare with BAST-24 results due to differences in methodology. Henkin's test measured detection and recognition of thresholds of taste and vapours, and it is worth noting the lack of thresholds validation as a limitation of the present study. Henkin's results showed a difficulty in olfaction in these nine patients, with thresholds for the vapours higher than normal

subjects. Lower score on smell forced-choice, and a tendency of lower score on detection and memory, was detected with BAST-24. In accordance with Henkin's data, the present study confirms the olfactory dysfunction in TS patients. Valkov [12] studied 20 patients with gonadal dysgenesis and abnormal karyotype (TS patients). Testing again for recognition and identification of vapour thresholds, he described anosmia, hyposmia and parosmia in 2, 3 and 7 patients respectively. A brief discussion speculated that TS karyotype often leads to changes in such structures as the formation reticularis, the hypothalamus, the limbic system or the auditory apparatus, which resulted in impairment of sensory functions. Unfortunately, these are individual cases with very low evidence.

A sub-analysis between monosomy (45X0) and other TS-karyotypes was performed in order to explore possible associations of olfactory function with karyotype [7,30]. No statistically significant differences were found in any olfactory characteristics between TS sub-groups, either sensory or sensitivity. The small number of patients involving pure monosomy and the great variety of karyotypes in the second group could limit the results of this sub-analysis.

The combination of smell (cranial nerve 1) and taste (cranial nerves 7, 9 and 10) defines the flavour perception of a food or beverage [31]. Therefore, the sense of taste was also studied in the present study. No differences were detected in BAST-24 gustometry outcomes when comparing TS patients with other hypogonadisms and controls. Analysing Henkin's results, for the 4 modalities of taste (sweet, salty, sour and bitter), elevated thresholds for bitter and sour in TS patients were found [11]. Although no statistically significant differences in taste domains were observed in the present study, a lower score tendency was found with sour powder in TS patients. Moreover, when the average percentage of correct answers from each group of patients was assessed, TS patients scored 91.7%, whereas the study's control group and the historical cohort almost obtained the maximum score (Table 3). In Valkov's study 5 patients were diagnosed with ageusia or hypogeusia, among 17 tested [12]. It may be possible that actual differences in taste sense exist between TS patients and control groups. However, a limited sensitivity of the gustometry section of BAST-24 without validated thresholds did not allow for detection. Taste appears to be more resistant because it is mediated by more than one cranial nerve and because of the compensation produced by inhibitory connections among the taste nerves [32]. Therefore, noticeable loss or distortion of the sense of taste is considerably less frequent than that observed for the sense of smell and differences between groups are more difficult to detect.

Disorders of smell and taste could still present a challenge to doctors, and their prognosis and management depend on the aetiology. Indeed, the pathophysiology of olfactory dysfunction found in TS patients is unknown, and imaging studies could be indicated to clarify possible causes. It is possible that a lack of olfactory tracts development exists as in patients with Kallmann's syndrome, a regression or partial formation of olfactory bulbs, or some alterations of the neuroepithelium.

In conclusion, impairment in smell sensory characteristics seems to exist in TS patients. While odour sensitivity does not seem to be affected in TS patients, sex hormones could have a role in smell intensity and irritability. Taste function does not appear to be altered in TS women, either detection or forced-choice, partially affecting flavour perception. Nevertheless, limitations of the BAST-24 gustometry test and the small number of TS patients for detecting a rare dysfunction such as taste alteration could hinder possible differences between groups. Further studies are needed to explore the mechanisms by which an impairment of sensory functions resulted among TS patients.

Contributors

CR and CCB took part in the patient's inclusion of the study, CR and SC carried out physical examination and BAST-24 olfactometry and gustometry test. IA and JM performed the nasal physical examination. CCB and JM designed the study. CR, IA, JB, JM and CCB took part in the analysis and interpretation of data, and revision of the draft.

Competing interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.maturitas.2012.07.012.

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5. TURNER'S SYNDROME AND OTHER CONGENITAL HYPOGONADISMS IMPAIR QUALITY OF LIFE AND SEXUAL FUNCTION

Turner's Syndrome And Other Congenital Hypogonadisms Impair Quality Of Life And Sexual Function.

Ros C, Alobid I, Balasch J, Mullol J, Castelo-Branco C.

GENERAL GYNECOLOGY

AQ: 1

AQ: 2

Turner's syndrome and other forms of congenital hypogonadism impair quality of life and sexual function

AQ: au   Cristina Ros, MD; Isam Alobid, PhD; Juan Balasch, PhD; Joaquim Mullol, PhD; Camil Castelo-Branco, PhD

OBJECTIVE: We sought to assess the burden of Turner's syndrome (TS) and other congenital hypogonadisms (OCH) on quality of life (QOL) and sexual function.

STUDY DESIGN: An observational study was undertaken in a gynecological endocrinology unit of a teaching hospital. Three cohorts of women aged 20-50 years were compared: 26 TS patients, 21 women with OCH and wild-type karyotype, and 41 healthy age-matched women who were included as controls. All subjects filled out the Medical Outcome Study Short Form (SF-36) and the Female Sexual Function Index.

AQ: 4

RESULTS: TS subjects had significantly worse QOL scores in physical functioning ($P = .026$) and role physical functioning ($P = .032$) whereas OCH showed significantly worse scores in physical functioning ($P = .027$) and bodily pain ($P = .025$) compared to controls. In all, 80%

of OCH and 50% of TS patients declared sexual activity. Sexually active TS patients had poorer arousal outcomes ($P = .009$) and OCH women showed significantly worse scores in arousal ($P = .002$), orgasm ($P = .007$), pain ($P = .001$), and Female Sexual Function Index total score ($P = .004$) compared with healthy controls. No differences between sexually active and inactive TS women were found in SF-36 scores, clinical characteristics, or anthropomorphic characteristics.

CONCLUSION: TS and OCH subjects presented impaired physical domains in QOL. Women with TS are less likely to be involved in sexual activity, arousal dysfunctions being their main symptom. Conversely, arousal, orgasm, pain, and total score were significantly affected in OCH subjects.

Key words: hypogonadisms, quality of life, sexuality, Turner's syndrome

T urner's syndrome (TS) is a genetic disorder that affects 1 in 2500 females, characterized by the total or partial absence of one of the X chromosomes. The main characteristics of TS are short stature and gonadal dysfunction, as well as dysmorphic features varying in severity that may affect quality of life (QOL). In addition, increased morbidity is caused by the association of TS with some medical conditions such as cardiac and renal malformations, hypothyroidism, osteoporosis, diabetes mellitus, and hearing disturbances.[1-4]

Although intelligence quotient and verbal abilities are usually normal, some subjects with TS show impaired spatial-numerical processing or disabilities affecting recognition or executive functions.[5,6] Depression is the most prevalent psychiatric diagnosis in TS adults compared with the general population; however, TS subjects demonstrate more shyness, social anxiety, and low self-esteem than those without TS.[7] This profile leads to weaker social relationships and poorer school performance.[8] Despite this psychosocial profile and medical complaints, young women with TS reported normal health related to QOL when they had an age-appropriate induced puberty and had reached normal height.[9,10] A few reports have suggested

that sexual function (SF) is impaired in women with TS.[11,12]

Similar psychosocial difficulties have been reported in women with other forms of congenital hypogonadisms (OCH) and 46,XX karyotype, without either physical dysmorphology or neurocognitive dysfunctions.[13,14] Therefore, whether these difficulties are caused by the effects of X chromosome deletion or early ovarian failure is a question pending resolution.

Remarkably, to our knowledge, no previous studies exist where TS women were compared with OCH in terms of QOL and sexual function. Based on this understanding, the current investigation was undertaken to address this subject using TS patients, in addition to 2 appropriate comparator groups: OCH and a control group taking exogenous hormones. The aim of this study was to assess the burden of TS on QOL and sexual function in adult women using generic (Medical Outcome Study Short Form-36) and specific (Female Sexual Function Index [FSFI]) QOL questionnaires, compared to OCH and control groups.

TABLE 1
Clinical characteristics of study population

Characteristic	Controls (n = 41)	TS (n = 26)	OCH (n = 21)
Patients completing SF-36	41 (100)	26 (100)	21 (100)
Patients completing FSFI	41 (100)	13 (50)	17 (81)
Age, y	34.6 ± 7.2	36.7 ± 8.4	34.3 ± 8.9
Weight, kg	60.8 ± 11.0	56.6 ± 11.6	63.3 ± 13.3
Height, cm	163.3 ± 5.3	149.1 ± 21.8	162.0 ± 25.2
Age at diagnosis, y	—	11.1 ± 10.1	18.4 ± 10.2
Age of menarche, y	12.3 ± 1.3	18.2 ± 5.4	17.8 ± 3.2
Patients with spontaneous menarche	41 (100)	13 (50)	11 (52)
Patients with comorbidities[a]	7 (17)	18 (69)	9 (43)
Patients with stable partner	35 (85)	10 (38)	6 (38)

Results are expressed as total numbers (percentages) and as mean ± SD.

FSFI, Female Sexual Function Index; *OCH*, other congenital hypogonadisms; *SF-36*, Medical Outcome Study Short Form; *TS*, Turner's syndrome.

[a] Including high blood pressure, hypothyroidism, dyslipemia, hypertransaminasemia, osteoporosis, diabetes mellitus, renal or cardiac malformations.

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MATERIALS AND METHODS
Patients

A total of 47 women aged 20-50 years presenting primary amenorrhea were included in this prospective cohort study from June 2010 through July 2011. According to the American Society for Reproductive Medicine criteria,[15] patients had TS or OCH.

TS women (n = 26) were included as the first cohort. TS diagnosis was done by blood sample karyotype showing total or partial absence of X chromosome in, at least, >10% of leukocytes. All women were receiving hormone replacement therapy (HRT) for the development of secondary sexual characteristics and to maintain feminization. Sequential preparations of estradiol hemihydrate 2 mg/1 mg and 1 mg of norethisterone acetate were used.

Women with OCH (n = 21) were selected as the second cohort. Seven women had pure gonadal dysgenesia 46XX (hypergonadotropic hypogonadism), and 14 had idiopathic hypogonadotropic hypogonadism, including Kallmann syndrome. These patients were similarly receiving the same HRT due to their congenital hypoestrogenism.

Nonexposed age-matched women were included as the control group (n = 41). All of them were being treated with estrogen and progestin for contraception, menstrual cycle regulation, or mild primary dysmenorrhea. To build the age-matched group, TS patients were sorted in 5-year groups, and the control women were recruited to meet the percentage of patients of these 5-year groups. They were recruited at our gynecological outpatient area, and none were taking any other drug or had any disorder that could have altered the study results. Inclusion criteria in the control group were people taking hormonal contraception in order to avoid possible bias related to exogenous hormones.

All patients were monitored using FSH, LH, and estradiol blood determination to make sure they were being supplemented with an adequate dose of estrogen, and only subjects with >1 year of HRT or contraception were included.

Study design

An analytical study of 3 independent cohorts was designed: TS, OCH, and controls. All subjects were asked to fill out validated questionnaires on health-related QOL and sexual function during a routine visit in the outpatient area. They received diagnosis and follow-up at the Endocrinological Gynecology Unit of Hospital Clinic of Barcelona. Subjects were informed of the study's characteristics, and the data obtained from questionnaires would be entered into a database with an identifier code, ensuring the patients' anonymity. Women who agreed to participate signed informed consent, and completed the questionnaires alone without assistance.

QOL questionnaires

The Medical Outcome Study Short Form-36 (SF-36) is a generic QOL questionnaire that has been adapted for the Spanish-speaking general population with good reproducibility and validity.[16,17] The questionnaire SF-36 contains 36 self-administered questions developed to measure health status in 8 domains, covering both physical and mental health. The physical component summary includes 4 domains: physical functioning (10 questions), role physical functioning (4 questions), bodily pain (2 questions), and general health (5 questions). The mental component summary includes 4 domains: vitality (4 questions), role emotional functioning (3 questions), social functioning (2 questions), and mental health (5 questions). Domain scores range from 0-100, with higher scores showing a better health status. SF-36 was scored according to the equivalence of SF-36 summary health scores estimated using standard and country-specific algorithms in Spain, following the results from the International QOL Assessment Project.[18,19] The results for each domain were calculated to give an average score for each. Afterward the result of the domain was normalized by subtracting the average of the Spanish population and dividing by its SD.

The FSFI is a multidimensional self-reporting instrument for the assessment of the key dimensions of female sexual function in clinical and nonclinical samples. This questionnaire contains 19 items assigned to 6 sexual domains: desire (2 questions), arousal (4 questions), lubrication (4 questions), orgasm (3 questions), global satisfaction (3 questions), and pain (3 questions). Every

item has multiple-choice answers (ranging from 0 = poor sexual status to 5 = good sexual status), with a maximal total score of 36 points. The individual domain scores of the FSFI are derived by a simple computational algorithm. The final score is obtained by adding the 6 domain scores.[20]

Main outcome measures

The main outcome measurements were the results of each domain and total score of SF-36 and FSFI questionnaires. All patients included in the study answered the SF-36 questionnaire, whereas only sexually active patients filled out FSFI questionnaire. Additionally, other variables were collected: age, anthropometric characteristics, spontaneous menarche, and ages at diagnosis and at the beginning of HRT. In the present study, patients with spontaneous menarche at <16 years of age (and consequently, spontaneous development of secondary sexual characteristics) or age at diagnosis <16 years (and consequently, with the beginning of estrogen replacement therapy at age <16 years) were considered patients with normal puberty. The presence of dysmorphic features was also evaluated in TS patients. Mild features included short stature, cleft palate, genu valgum, and low-set ears. Pterygium coli, short neck, short extremities, and syndromic facies were considered as severe features. Finally, TS-associated comorbidities were collected, such as hearing loss, cardiac and renal malformations, diabetes, hypothyroidism, osteoporosis, high blood pressure, or dyslipemia.

Statistical analysis

Data were analyzed using SPSS 19.0 for Windows (SPSS, Inc, Cary, NC). Descriptive analysis was expressed in frequencies and percentages (qualitative variables) or reported as mean and SD (quantitative variables). Normality was assessed by the Kolmogorov-Smirnov test. As our data were not normally distributed, nonparametrical tests were used, differences between groups being analyzed by the Mann-Whitney U test. Considering the presence of sexual activity in TS patients, comparisons between

subgroups of noncontinuous variables were performed using a χ^2 homogeneity test. A P value < .05 was considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Ethics Committee of the Hospital Clinic of Barcelona (October 28, 2010) and was performed in accordance with the Helsinki II Declaration and the ICH Guidelines for Good Clinical Practice. All women provided their written informed consent and participated voluntarily in the study.

RESULTS

Clinical and anthropometrical characteristics of the subjects are shown in Table 1. As expected, controls and OCH patients were taller than TS patients, and only 13 women with TS had spontaneous menarche. All women with TS who presented spontaneous menarche developed ovarian failure at age <30 years

FIGURE 1
Comparison of SF-36 domain outcomes for control group, TS patients, and women with OCH
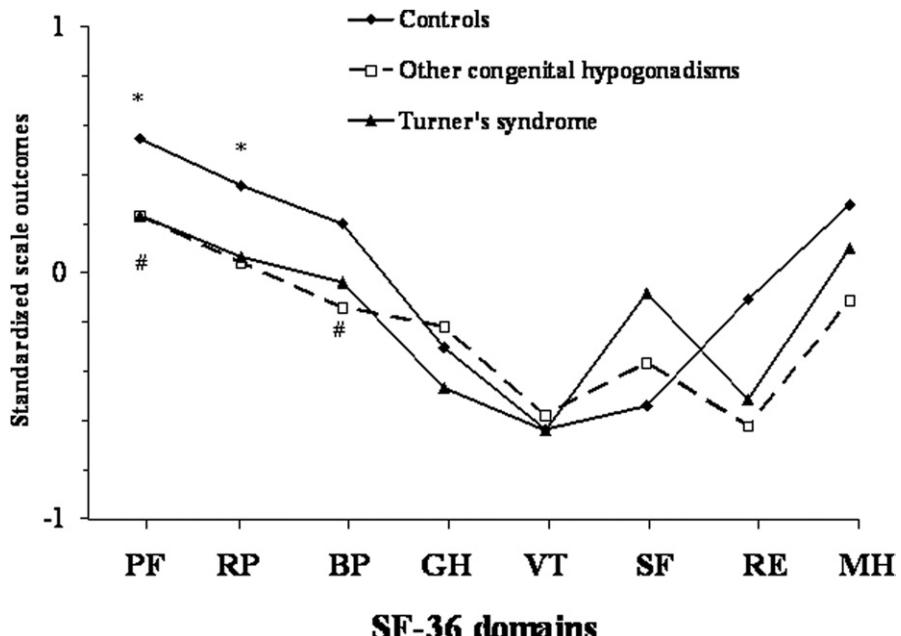
P < .05 statistically significant differences between *TS or #OCH and control group in Mann-Whitney U test.

BP, bodily pain; *GH,* general health; *MH,* mental health; *OCH,* other congenital hypogonadisms; *PF,* physical functioning; *RE,* role emotional functioning; *RP,* role physical functioning; *SF,* social functioning; *SF-36,* Medical Outcome Study Short Form; *TS,* Turner's syndrome; *VT,* vitality.

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(mean time of spontaneous menses 7.1 ± 6.4 years). All controls had menarche at age <16 years, whereas the mean age of spontaneous or induced menarche among TS subjects was 18.2 years. Finally, up to 69% patients with TS experienced comorbidities, such as high blood pressure, hypothyroidism, dyslipemia, osteoporosis, or diabetes mellitus.

All subjects (100%) filled out the SF-36 questionnaire. TS subjects show significantly worse QOL scores in physical functioning (P = .014) and in role physical functioning (P = .038) compared to the control group. Significant differences were not found in either the mental component summary, or in any mental individual domain (Figure 1). On the other hand, OCH presented worse scores in physical functioning (P = .05) and bodily pain (P = .041) compared to the control group. No differences between TS and OCH were found in any domain or SF-36 summaries (Figure 1).

FIGURE 2

Comparison of FSFI domain outcomes for control group, TS patients, and women with OCH

□ Controls   ■ Turner's syndrome   ▨ Other congenital hypogonadisms
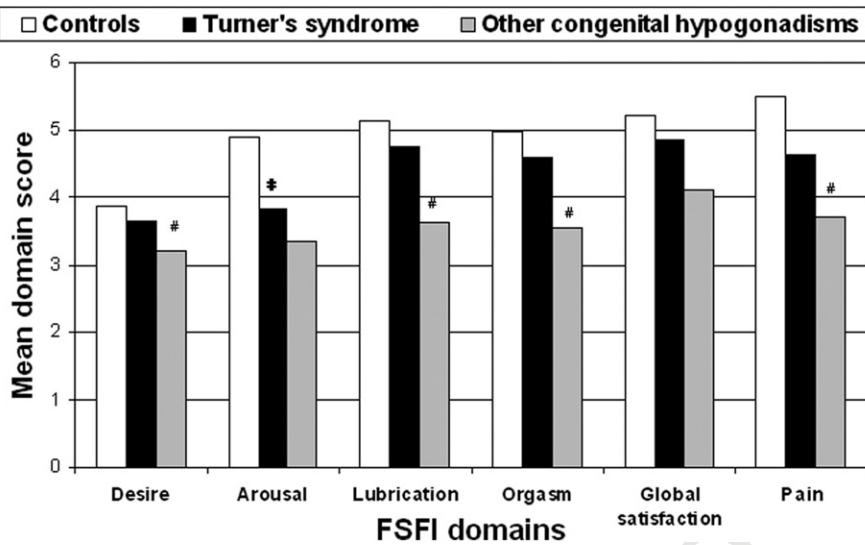
$P < .01$ statistically significant differences between *TS or #OCH and control group in Mann-Whitney U test.

FSFI, Female Sexual Function Index; OCH, other congenital hypogonadisms; TS, Turner's syndrome.

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In all, 80% of OCH but only 50% of TS patients declared sexual activity. Sexually active TS patients showed less satisfying arousal outcomes compared to the control group ($P = .009$). No differences were found in other domains or total score. However, in the OCH group, differences were found in arousal ($P = .002$), lubrication ($P = .13$), orgasm ($P = .007$), pain ($P = .001$), and total score ($P = .004$) when compared to the control group (Figure 2). No differences between TS subjects and the OCH group were found in FSFI domains.

Finally, the questionnaire scores of both sexually active and inactive TS patients were compared (Table 2). Considering height, patients without sexual activity were significantly shorter ($P < .05$) than those with sexual activity. Several analyses of sexual activity in subgroups of TS patients were performed (Table 2). Homogeneity tests were carried out to evaluate the burden of some TS features in sexual activity. In the present study, neither pubertal stage at age 16 years nor hearing status seemed to play a role in determining sexual activity. On the other hand, as expected, having a regular partner was associated with increased sexual activity among TS patients. Finally, the degree of dysmorphology and comorbidities had no statistically significant impact on FSFI scores ($P = .07$ and $P = .09$, respectively).

COMMENT

The main findings of the present study are: (1) women with congenital hypogonadisms (either TS or OCH) presented worse QOL than age-matched healthy women; and (2) hypogonadism is related to poor sexual functioning.

Data from previous studies suggest that TS women presented normal health-related QOL.[9,10] However, TS patients in our study scored worse QOL in 2 physical subscales of SF-36: physical functioning and role physical functioning. These results are in accordance with a recent study using the same questionnaire.[21]

Results from SF-36 were adjusted for age and final height, without significant differences between groups. These results differed from those observed by Naess et al[21] and Boman et al,[22] who concluded that the oldest and shortest women with TS reported more psychological distress and poorer health. The possible worsening of the QOL domains with age at diagnosis may be a result of the delay in the development of the secondary sexual characteristics due to the lack of estrogens. Comparing TS patients with normal puberty and TS patients with sexual development at age >16 years, no differences were found between groups in our study. However, an improved self-concept was defined in estrogen-treated TS adolescents compared with those who began hormone treatment at age >14 years.[10,23] Similar results were identified by Carel et al[24] in adult women with TS, with lower health-related QOL scores in patients with the induction of puberty at the age of >15 years. These findings highlight the need to initiate estrogen replacement therapy by ages 12-14 years in this population to achieve sexual pubertal development as well as healthy controls.

Dysmorphology stigmata (no TS features, mild features, or severe features) did not correlate with SF-36 scores in the present study, either the presence of hearing loss or comorbidities. In contrast, previous studies have shown correlations between hearing loss and almost all subscales of SF-36, but some other factors related to TS such as heart or thyroid dysfunction, blood pressure, and body size had no or little impact on QOL.[21,24,25]

Sexuality is an important domain in most of the QOL studies.[26] Despite the feasibility of laboratory-based physiological markers of sexual response, such as vaginal blood flow, it was proposed that the most valid way to assess sexual function in women was a self-report technique.[20] It is worth noting that self-reported data on sexuality diverge from those derived from a direct interview.[27]

Only half of TS patients in this study reported having any type of sexual activity and one-third declared being in a partner relationship. This figure is similar to that observed by Sheaffer et al[12] in the National Institutes of Health natural history study. In addition, only sexually active TS patients presented worse scores in arousal outcomes compared with controls. Consequently, their overall evalua-

TABLE 2
Characteristics of sexually active TS patients

Characteristic	Sexually active (n = 13)	Sexually inactive (n = 13)	P value
Age, y, mean ± SD	37.2 ± 7.6	36.3 ± 7.7	NS[a]
Height, cm, mean ± SD	152 ± 8.7	146 ± 5.6	.05[a]
Sexual activity of TS patients in subgroups according to Turner dysmorphology, n (%)			
Patients with major[b] stigmata (n = 7)	2 (29)	5 (71)	.07[d]
Patients with minor[c] stigmata (n = 15)	7 (47)	8 (53)	
Patients without stigmata (n = 4)	4 (100)	0 (0)	
Sexual activity of TS patients in subgroups according to Tanner stage at 16 y, n (%)			
Tanner stage ≥ III at age >16 y (n = 11)	4 (36)	7 (64)	NS[d]
Tanner stage ≥ III at age <16 y (n = 15)	9 (60)	6 (40)	
Sexual activity of TS patients in subgroups according to partner stability, n (%)			
Nonstable partner (n = 16)	3 (19)	13 (81)	< .0001[d]
Stable partner (n = 10)	10 (100)	0 (0)	
Sexual activity of TS patients in subgroups according to hearing status, n (%)			
Patients with normoacusia (n = 12)	6 (50)	6 (50)	NS[d]
Patients with hypoacusia (n = 14)	7 (50)	7 (50)	
Sexual activity of TS patients in subgroups according to comorbidities, n (%)			
Patients without comorbidities (n = 8)	6 (75)	2 (25)	.09[d]
Patients with comorbidities (n = 18)	7 (39)	11 (61)	

NS, no significant differences; *TS*, Turner's syndrome.

[a] *t* test; [b] Pterygium coli, short neck, short extremities, syndromic facies; [c] Short stature, cleft palate, genu valgum, low-set ears; [d] Homogeneity χ^2 test.

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tion of the sexual activity could be considered satisfying. These results are in agreement with other studies, which demonstrated that TS subjects in a partner relationship reported relatively normal overall sexual function, but those without partners declared very low-level sexual functioning.[12,28]

Conversely to TS subjects, large differences were encountered when comparing OCH women with controls in most of the domains and in total score. These results could be interpreted as an important complaint of these patients regarding their sexual life, and although HRT is standard for women with premature ovarian failure at age <50 years, pharmacological hormone regimens do not fully mimic natural steroids production.[29] It could be thought that TS women should therefore present similar results in FSFI. However, OCH are patients not related with dysmorphology or psychosocial difficulties, as reported in TS patients.[7,8] Thus, OCH only bear dys-

functions linked to the lack of hormones, as sexual function, and not having any other comorbidity like TS patients whose main concern is not their sexual activity.

Height, age, physical stigmata, estrogen use, age of puberty, and hearing loss may affect sexual function. In our series, TS patients without sexual activity were significantly shorter than patients with sexual activity. Nevertheless, no significantly differences between groups were found in the clinical characteristics mentioned above. These results are in agreement with those of Sheaffer et al,[12] but differ from those of Carel et al,[24] who concluded that height and dysmorphic features were not associated with sexuality, self-esteem, or social adjustment.

In our series, age at diagnosis or the presence of spontaneous menarche were not related to impairment in sexual function in TS, which is in agreement with other studies.[12,24,30] Other potential sources of sexual difficulties in TS may

include stigmatization because of dysmorphological features. However, in concordance with Sheaffer et al,[12] these data were not corroborated in the present study. In spite of cardiac involvement being associated with later sexual debut,[24] no differences were found among patients with and without cardiac malformations, or in the presence or absence of other comorbidities such as renal malformations, high blood pressure, hypothyroidism, dyslipidemia, diabetes mellitus, hypertransaminasemia, osteoporosis, or hearing disorders.

Some limitations exist in the present study such as the low sample size, which suggest that the results should be interpreted with caution. For instance, 50% of the TS patients did not fill out the sexual questionnaire because they had never had any type of sexual activity. It is worth noting that this aspect is an interesting result, since questionnaires were offered to all women with TS during the medical visit instead of being mailed. The main

limitation found in previous studies was the low response rate to the postal questionnaire, which would lead to selection bias, and besides, it did not show the reason for the low response rate. The FSFI was firstly validated in Spanish language for Chilean population,[31] but this version had not been tested in Spanish native women. Therefore, a specialized medical writer was contacted to carefully translate the validated English version[20] into Spanish language. This version that was identical to the previous Spanish version[31] was tested in 10 volunteers showing no comprehension difficulties.

Conclusion

TS patients declared worse QOL in physical domains and a lower average of sexual intercourses and frequency of sexual partnering. However, the poor sexual functioning was not correlated with specific hormonal or genetic features of the syndrome, and among those with partners, sexual functioning seemed normal. In contrast to TS, OCH showed low scores in almost all sexual domains. These results should make health care providers consider devoting more time and effort to support these patients. Ideally, practitioners should initiate discussions regarding puberty, sexual functioning, and reproductive options during pediatric attention and continue the psychosocial education during pubertal development and sexual maturation. ∎

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4. RESUM DE RESULTATS I DISCUSSIÓ

Correlacions entre el cariotip i el fenotip

Es van incloure a l'estudi un total de 27 pacients entre 20 i 50 anys, diagnosticades de ST mitjançant un cariotip en sang realitzat segons la tècnica estàndard (comptatge entre 15-30 metafases). Es va realitzar un nou cariotip en dos teixits de diferent estirp: un nou estudi en sang, comptant 50 limfòcits-T (mesoderm); i un cariotip en orina, amb la intenció de comptar 50 cèl·lules urotelials (endoderm).

Els cultius d'orina de 12 pacients (44% de les mostres) van ser contaminats per microorganismes (fongs i cocs), essent la majoria d'ells irrecuperables. A més, no en tots els casos va ser possible comptar les 50 metafases esperades degut a l'escassa cel·lularitat. El cultiu d'orina precisa de l'administració immediata del medi de cultiu Chang després de l'obtenció de la mostra, i d'un ràpid processament (primera centrifugació en la primera hora). A més, són necessàries 3-4 setmanes pel seu creixement, i les bandes dels cromosomes tenen una menor resolució que les obtingudes a partir dels limfòcits (13).

Quan es va augmentar el comptatge de metafases fins a 50, es van identificar 3 mosaïcismes críptics, que no apareixien en els cariotips antics. Aquesta troballa va en concordància amb la teoria que indica que és necessària una línia de mosaic per a la supervivència del fetus (11, 12), i aquesta és més fàcil de trobar comptant més metafases. Un d'ells incloïa una línia amb isocromosoma, que reforça l'hipotiroïdisme que presenta la pacient; l'altre, un cromosoma en anell. No obstant, el cas més interessant va ser l'aparició d'una línia cel·lular amb cromosoma Y, que va suposar un canvi d'actitud realitzant una gonadectomia a la pacient per evitar el risc de gonadoblastoma (16, 67). No obstant això, el recompte de 50 cèl·lules és particularment interessant en l'estudi de les dones amb insuficiència ovàrica prematura oculta, que sovint consulten en relació amb problemes de fertilitat. La detecció d'un mosaïcisme críptic amb algunes metafases amb monosomia 45, X podria explicar la seva infertilitat (36).

Comparant els cariotips en els dos teixits, sis pacients amb mosaïcismes al cariotip de sang van mostrar una monosomia pura al cariotip en orina. Línies que presentaven cromosomes en anell o isocromosomes en sang, no es van expressar en orina. El cromosoma que es perd amb més facilitat en dones és el

cromosoma X, i les cèl·lules que provenen de l'endoderm, són més inestables que els limfòcits T (68). Això suposa una pèrdua d'informació cromosòmica respecte la sang, que empitjora la relació genotip-fenotip.

La majoria de gens responsables de la talla baixa, la dismorfologia, la disgenèsia gonadal i les malformacions cardíaques i renals estan presents al braç curt del cromosoma X (17, 69). Per tant, les pacients amb monosomia pura i amb isocromosoma del braç curt del cromosoma X han estat considerades en el mateix grup. Existeixen correlacions entre el cariotip en sang i l'antecedent de menarquia espontània, l'alçada, els trets de dismorfologia, i les malformacions congènites cardíaques i renals en les pacients estudiades. Igualment, l'hipotiroïdisme es correlaciona amb la presència d'isocromosoma, en monosomia o mosaïc (70, 71). Aquestes correlacions no apareixen en l'anàlisi del cariotip en orina degut a la pèrdua de cromosomes X alterats.

Tenint en compte aquests resultats, es conclou que l'anàlisi de metafases de limfòcits T a partir d'una mostra de sang segueix essent la tècnica de referència per a l'estudi del cariotip. Es recomana augmentar el recompte de cèl·lules fins a 50 si se sospita una disgenèsia gonadal o una fallida ovàrica prematura. Així s'augmenta la detecció de mosaïcismes críptics que poden condicionar canvis de conducta.

El cultiu de cèl·lules urotelials a partir de mostres d'orina presenta dificultats i limitacions tècniques, a més d'una pèrdua d'informació cromosòmica que empitjora la seva correlació amb el fenotip.

Pèrdua auditiva a la ST a l'edat adulta

Es va realitzar un test auditiu a tres cohorts de pacients: un grup d'estudi de 31 dones diagnosticades de ST; i dos grups controls, de 15 dones amb altres hipogonadismes congènits (OCH) i cariotip normal i 41 dones sanes que prenien contracepció hormonal. Les dones amb hipogonadismes estaven prenent tractament hormonal substitutïu amb estrògens i progestàgens.

L'estudi auditiu incloïa una història clínica dirigida, una micro-otoscòpia, una audiometria tonar estàndard (prova subjectiva), i uns potencials evocats auditius (prova objectiva).

Fins un 87% de dones amb ST presentaven en els audiogrames algun grau de pèrdua auditiva, en comparació amb el 20% dels controls sans i el 27% dels OCH. Els potencials evocats auditius (BAEP) van ser patològics en el 61% de les dones amb ST, presentant-se alterats en només un 20% dels OCH. Aquestes diferències entre les audiometries i els potencials evocats s'expliquen per una major objectivitat en la segona prova diagnòstica, i els resultats coincideixen amb altres estudis publicats (40, 47).

Analitzant els resultats dels BAEP, no hi va haver diferències significatives en l'anàlisi de les latències, amplituds i interlatències de les ones I, III i V entre les dones amb ST i les OCH, ni tampoc comparant els resultats amb la població de referència. Altres estudis han reportat diferències en les latències absolutes entre les dones amb ST i els controls: alguns van trobar escurçaments (41); d'altres, latències prolongades (40, 73). Els autors d'aquests estudis no donen explicacions concloents a respecte.

L'hipoacúsia neurosensorial va ser el tipus més freqüent de pèrdua auditiva en les dones adultes amb ST del nostre estudi, amb graus superiors de gravetat si es comparen amb els dos grups controls. És difícil comparar els resultats del present estudi amb altres realitzats prèviament, doncs la majoria s'han fet en nenes amb ST, on el tipus d'hipoacúsia més freqüent és la de conducció (40, 44, 45, 72). En dones adultes, l'hipoacúsia neurosensorial o mixta és la més freqüent (41), d'acord amb els nostres resultats. Es coneix que l'incidència d'hipoacúsia neurosensorial s'incrementa amb l'edat (44), i es creu deguda a una disfunció coclear (41). A més d'una apoptosi accelerada de les cèl·lules de la còclea, també s'han reportat densitats de cèl·lules inferiors a l'òrgan de Corti en les dones amb ST (74).

Així, tant l'hipoacúsia de conducció con la neurosensorial es poden explicar per alteracions en el desenvolupament de les dones amb ST. La severitat de la dismorfologia va lligada amb l'alteració cariotípica (5, 50, 75), i alguns gens responsables del dèficit auditiu s'han localitzat al braç curt del cromosoma X

(42). Seguint aquestes premisses, les dones amb monosomia 45,X o isocromosoma del braç curt del X haurien de patir graus d'hipoacúsia més severs que les dones amb ST i altres cariotips. I el sub-anàlisi d'aquests dos grups va confirmar aquesta hipòtesi.

A més, es van analitzar altres sub-grups de dones amb ST. Es van observar pitjors resultats auditius en les pacients de major edat, d'acord amb la literatura (41, 42, 47). Igualment, també van presentar pitjors resultats les dones amb ST amb història d'otitis mitja recurrent a l'infància (40, 45).

No obstant, no es van trobar diferències entre dones amb antecedent de pubertat instaurada als 16 anys, i dones sense aquesta característica. Cal recordar que tampoc no es van trobar diferències entre les dones amb OCH i els controls sans. Aquestes dues troballes permeten posar en dubte el paper dels estrògens sobre l'hipoacúsia. Estudis d'investigació bàsica han trobat receptors d'estrògens a l'oïda interna d'animals i humans (76, 77). Altres autors havien trobat millora en els resultats del BAEP en rates ooforectomitzades després d'una teràpia hormonal (78). Aquests resultats van originar estudis comparatius entre nenes amb tractament hormonal i sense teràpia, concloent que les nenes no tractades durant l'infància presentaven pitjors resultats auditius a l'edat adulta (49, 72). Els nostres resultats no semblen anar en aquesta direcció. L'hipoestrogenisme i el tractament hormonal substitutiu semblen tenir un paper secundari en la pèrdua auditiva, però es necessita més recerca per corroborar aquesta afirmació amb més fermesa.

Igualment, el tractament amb hormona de creixement tampoc no sembla tenir un impacte sobre l'hipoacúsia, tot i existir resultats contradictoris a la literatura (47, 48, 72).

En conclusió, una pèrdua auditiva progressiva precoç s'associa a la ST, essent l'hipoacúsia neurosensorial el patró més freqüent en les dones adultes. L'etiologia d'aquesta hipoacúsia és heterogènia, i l'edat, la genètica i l'antecedent d'otitis mitjana crònica recurrent durant la infància són factors influents.

Actualment, l'única actuació mèdica de prevenció primària útil per a disminuir la taxa d'hipoacúsia en aquestes pacients és el tractament agressiu de l'otitis mitjana durant l'infància, i evitar les recurrències.

Alteracions olfactòries i gustatives a la ST

Amb l'objectiu d'avaluar d'impacte de la ST i altres hipogonadismes congènits en el sentit de l'olfacte i el gust, es va dissenyar un estudi amb tres cohorts independents: un grup de 30 dones amb ST, entre 20 i 50 anys, que prenien teràpia estroprogestagènica de substitució; un altre de 14 dones diagnosticades d'altres hipogonadismes congènits amb cariotip normal, tractades amb la mateixa teràpia que el primer grup; i finalment, un grup de 43 dones sanes que prenien anticonceptius hormonals.

Totes les pacients van ser sotmeses a una història clínica rinològica, una endoscòpia nasal, i l'avaluació de l'olfacte i el gust mitjançant el test validat *Barcelona Smell Test 24* (BAST-24).

Per tal de validar el grup control de l'estudi, les dones sanes que prenien contraceptius van ser comparades amb una cohort històrica de 40 dones sense cap tractament hormonal, que havia estat estudiada per a la validació del BAST-24 a l'Hospital Clínic de Barcelona. Comparant els resultats de l'olfactometria, les dones que prenien anticonceptius hormonals van sentir les olors amb major intensitat i menys irritabilitat que les pacients de la cohort històrica. No es van trobar diferències en altres paràmetres sensitius (frescor o plaer) ni sensorials (detecció, memòria i reconeixement) olfactoris. Aquests resultats recolzen que la sensibilitat olfactiva està influenciada per les hormones sexuals (53, 79, 80). No obstant això, altres estudis no han trobat una influència hormonal en el sentit de l'olfacte (81, 82, 83). Fins que la literatura resolgui aquest tema, pensem que un grup control amb teràpia hormonal és l'idoni per a l'actual estudi.

Les pacients amb ST van presentar pitjor resultats en el reconeixement de les olors, en comparació amb els controls que prenien anticonceptius. No es van trobar diferències en els paràmetres de la sensibilitat olfactiva entre els tres grups. Aquests resultats confirmen l'alteració olfactòria que es postulava en els

dos únics estudis publicats a l'any 1967 (54) i al 1975 (55), tot i que no podem aportar dades sobre la fisiopatologia que explica aquest fet. És difícil la comparació directa entre els nostres resultats i els dos estudis anteriors, degut a l'ús de test molt diferents degut a l'ampli interval de temps.

No hi va haver diferències en el percentatge de fumadores entre els 3 grups d'estudi, ni l'incidència de rinitis al·lèrgica o asma. Igualment, l'exploració oronasal va ser similar en els 3 grups. Per tant, sabem que les causes més freqüents d'obstrucció nasal i hipòsmia que presenta la població general (52) no van alterar els resultats del present estudi. Tampoc no hi va haver diferències entre grups de pacients amb ST i diferents alteracions cariotípiques.

La combinació entre l'olfacte i el gust defineix el sabor. Per tant, l'estudi es va completar amb una gustometria. Els tres grups d'estudi van detectar els quatre gustos del test, sense diferències a l'hora d'analitzar la taxa d'encert dels mateixos de forma individual. Els estudis de Henkin (54) i Valkov (55) van detectar cert grau d'hipogèusia en dones amb ST, tot i que els tests gustomètrics es basaven en la detecció de llindars de gustos. La gustometria que inclou el BAST-24 no treballa amb llindars, i per tant, és una limitació del present estudi. Podem dir que, encara que sense significància estadística, els resultats de les pacients amb ST són pitjors que els dos grups controls, i no descartem que existeixin alteracions en el sentit del gust associades a la ST. Malgrat això, la freqüència de les alteracions del gust és molt inferior a les alteracions auditives o olfactòries, i les diferències entre grups són més difícils de cercar. La baixa mostra del present estudi limita les conclusions que es poden treure a respecte.

Per tant, existeix un deteriorament sensorial olfactori en les pacients amb ST, tot i que la seva fisiopatologia reman desconeguda. Malgrat que la sensibilitat olfactòria no sembla afectada en aquestes pacients, les hormones sexuals tenen un paper en la percepció de la intensitat i la irritabilitat de les olors.

No semblen existir alteracions en el sentit del gust en les pacients amb ST i altres hipogonadismes congènits.

Deteriorament de la qualitat de vida i la funció sexual a la ST i altres hipogonadismes congènits

Dos qüestionaris van ser utilitzats per analitzar l'impacte de l'hipoestrogenisme congènit i d'altres comorbiditats associades a la ST sobre la qualitat de vida i la funció sexual: el *Medical Outcome Study Short Form-36* (SF-36); i el *Female Sexual Function Index* (FSFI). De nou, es van seleccionar tres grups de pacients: 26 pacients amb ST, entre 20 i 50 anys, en teràpia hormonal substitutiva amb estrògens i progestàgens; un segon grup de 21 pacients amb altres hipogonadismes congènits i cariotip normal (OCH), també amb medicació hormonal de substitució; i un tercer grup de 41 dones sanes amb contracepció hormonal combinada.

Les dones amb ST van mostrar pitjors puntuacions que els controls en el SF-36 en dos sub-escales físiques: la funció física i el rol físic. No es van trobar diferències entre aquests dos grups en els dominis mentals. Igualment, les dones amb OCH van puntuar pitjor en la funció física i la percepció dolorosa, comparant-les amb els controls sans. No hi va haver diferències entre les dones amb ST i OCH. A la literatura, existeixen resultats contradictoris respecte aquest ítem. Mentre alguns estudis conclouen que les dones amb ST presenten pitjors resultats en els qüestionaris de qualitat de vida (84), d'altres no han trobat diferències respecte controls sans (61, 62).

No es van trobar diferències en els resultats del SF-36 entre sub-grups de dones amb ST tenint en compte l'edat, la talla, els trets dismorfològics, la pubertat instaurada abans dels 16 anys o la presència de comorbiditats associades. De nou, diversos autors han descrit prèviament una pitjor qualitat de vida en dones amb ST de major edat i menor talla (84, 85), o en adolescents que van començar la teràpia estrogènica després dels 14 anys i van patir una pubertat retardada (56, 62). Finalment, també s'han reportat pitjors resultats en dones amb ST i trets dismorfològics més severs, o altres comorbiditats associades (84, 86, 87). En el present estudi no trobem aquestes diferències entre sub-grups de dones amb ST, tot i que la baixa mostra és una limitació important.

Tanmateix, dades rellevants i interessants s'han trobat en el present estudi en l'àmbit de la sexualitat. En primer lloc, només un 50% de les dones amb ST explicaven tenir algun tipus d'activitat sexual, i un terç referia tenir una parella estable. Entre les dones amb ST sexualment actives, només puntuaven pitjor en el FSFI que els controls sans en l'excitació. S'ha comentat que la millor manera d'avaluar la funció sexual és mitjançant qüestionaris (88), i el present estudi evita biaixos freqüents d'altres estudis que utilitzen el correu postal o la via telefònica. Per tant, la baixa xifra d'activitat sexual entre dones amb ST presenta gran validesa. Alhora, el fet que les dones amb ST sexualment actives presentin resultats prou bons en els qüestionaris de sexualitat és una dada que concorda amb la literatura publicada (64, 89). Sembla que la sexualitat està en un segon àmbit, en dones amb tanta pluripatologia.

Contràriament, les dones amb OCH van presentar puntuacions clarament inferiors que els controls en quasi tots els dominis de la funció sexual (excitació, lubricació, orgasme, dolor, i puntuació global del FSFI). Això suggereix que, en dones amb hipogonadisme aïllat, sense dismorfologia ni altres comorbiditats associades, la sexualitat es troba notablement afectada malgrat el tractament substitutiu amb estrògens i progestàgens (90).

Finalment, les pacients amb ST van ser dividides i comparades en dos sub-grups segons la presència o absència d'activitat sexual. Tenint en compte l'alçada, les dones sense activitat sexual eren significativament més baixes. Ni l'antecedent del desenvolupament puberal finalitzat als 16 anys, ni la pèrdua auditiva, ni la presència de menarquia espontània, ni l'edat del diagnòstic de la síndrome, mostraven influència en la funció sexual. No obstant això, el grau de dismorfologia i les comorbiditats associades podrien jugar-hi un paper, tot i no estadísticament significatiu en el present estudi, en el deteriorament sexual associat a la ST. Sembla que aquests factors sí influeixen en la sexualitat, contràriament als resultats obtinguts en els paràmetres de qualitat de vida. La literatura mostra resultats similars, amb influència sobre l'activitat sexual de la talla baixa (64), la dismorfologia (64), i les alteracions cardíaques i altres comorbiditats associades (86).

En conclusió, les pacients amb ST i altres hipogonadismes congènits presenten pitjors puntuacions ens els dominis físics dels qüestionaris de qualitat de vida, comparades amb controls sans.

Només la meitat de les dones amb ST refereixen mantenir qualsevol tipus d'activitat sexual. i, les sexualment actives, només puntuen baix en el domini d'excitació. La funció sexual no es correlaciona amb les característiques físiques o les comorbiditats associades a la ST, tot i que les dones sexualment actives presenten alçades superiors.

Les dones amb altres hipogonadismes congènits presenten puntuacions en gairebé tots els dominis de la funció sexual, malgrat el tractament hormonal.

Maneig de la ST a l'edat adulta

Les dones amb ST tenen un risc elevat de desenvolupar problemes de salut, des de la infància fins a l'edat adulta (1, 2, 4, 5). Després d'un diagnòstic prenatal o neonatal precoç, l'equip pediàtric especialitzat s'encarrega d'avaluar les malformacions congènites i comorbiditats precoces associades a la ST. Alhora, es segueixen les directrius per al tractament amb l'hormona del creixement, així com la teràpia estrogènica per al desenvolupament puberal.

Durant l'edat adulta, les dones amb ST han de ser referides a unitats especialitzades de Ginecologia Endocrinològica, per a garantir el diagnòstic i tractament de trastorns que debuten o s'accentuen a l'edat adulta, com les alteracions metabòliques, immunològiques i neurosensorials. Cal garantir un tractament hormonal substitutiu adient fins a l'edat esperada de la menopausa, així com un consell sexual i reproductiu.

Avantatges i limitacions globals dels estudis

Una de les novetats que presenten aquests estudis respecte els anteriorment publicats a la literatura, és el reclutament d'un grup amb hipogonadismes congènits amb cariotip normal (tant hipogonadismes hipogonadotrops com hipergonadotrops). Juntament amb un grup de dones sanes prenent contracepció hormonal, els estudis permeten redactar conclusions sobre el

possible rol de l'hipoestrogenisme i el de les alteracions cromosòmiques en les comorbiditats estudiades.

Per una altra banda, totes les pacients amb hipogonadismes estan reclutades a partir de la consulta de Ginecologia Endocrinològica, i no des de les consultes d'Otorrinolaringologia. Així s'han evitat possibles biaixos sobre les dades de prevalença i gravetat dels símptomes. Igualment s'ha evitat el reclutament per correu postal i per via telefònica.

La principal limitació dels estudis derivats d'aquest projecte de tesi és el baix tamany mostral, que suggereix la interpretació dels resultats amb cautela. Cal tenir en compte que la ST i altres hipogonadismes congènits són malalties minoritàries a tot el món; per tant, les grans sèries són difícils d'obtenir. No obstant això, a l'era actual del meta-anàlisi, proporcionar resultats d'estudis ben dissenyats, tot i amb baixa potència, pot ser d'utilitat. Aquests estudis tenen com a objectiu estimular el disseny de nous projectes amb un poder estadístic més elevat, probablement assajos multicèntrics, per tal d'abordar aquesta qüestió i aclarir-ne les controvèrsies.

5.   CONCLUSIONS

Les dones amb ST mereixen una atenció multidisciplinària especialitzada a l'edat adulta degut a les comorbiditats associades que presenten.

Degut a l'alta prevalença d'hipoacúsia precoç, es recomana incorporar una audiometria periòdica en el protocol de seguiment de les dones amb ST durant la vida adulta. Així serà possible la identificació de la presbiacúsia accelerada i sovint, desapercebuda, que presenten aquestes pacients.

Existeixen alteracions de sensorialitat olfactòria associades a la ST, de fisiopatologia desconeguda.

El deteriorament de la qualitat de vida i la funció sexual de les dones amb ST i altres hipogonadismes congènits suposa la necessitat d'un abordatge per part dels professionals sanitaris, assegurant el desenvolupament puberal, comentant les alteracions de la funció sexual, i oferint les diferents opcions reproductives a aquestes pacients.

Existeix una correlació parcial entre el cariotip en sang i el fenotip, tot i que es requereix més recerca citogenètica per a identificar els gens responsables de les comorbiditats i característiques associades a la ST.

Implicacions clíniques

- Cal comptar fins a 50 metafases en els estudis citogenètics en sospita de fallida ovàrica.
- Cal fer audiometries periòdiques a la ST durant l'edat adulta.
- Cal investigar la qualitat de vida i la funció sexual de les pacients amb hipogonadismes.
- Es recomana que les pacients amb hipogonadismes congènits es visitin en unitats especialitzades.
- Cal garantir un tractament hormonal substitutiu adient per les pacients amb hipogonadismes fins a l'edat esperada de la menopausa, així com un cosell sexual i reproductiu.

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7. ANNEXES

S'han afegit en aquest apartat els següents documents que poden ser d'utilitat:

- full de recollida de dades de ginecologia.

- full de recollida de dades d'otorrinolaringologia.

- test d'olfactometria-gustometria *Barcelona Smell Test 24* (BAST-24), utilitzat a l'article número 4.

- qüestionari de qualitat de vida *Medical Outcome Study Short Form-36* (SF-36), utilitzat a l'article número 5.

- qüestionari de sexualitat *The Female Sexual Function Index* (FSFI), traduït a l'espanyol (article número 5).

FULL DE RECOLLIDA DE DADES DE GINECOLOGIA

HIPOGONADISMOS CONGÉNITOS: PROTOCOLO CLÍNICO GINECOLOGÍA

Código: ....

Fecha exploración: ....

RECOGIDA DATOS

1. Anamnesis:

2.1. Diagnóstico:
☐ 0 Control (no expuesto)
☐ 1 Sd Turner
☐ 2 Sd Kallmann
☐ 3 Disgenesia gonadal 46XX
☐ 4 Disgenesia gonadal 46XY

2.2. Antecedentes personales:
Grupo étnico:
Edad diagnóstico:

Cariotipo: ☐ 46XX   ☐ 45X0   ☐ 45X/46XX
               ☐ 46X/46XiXq   ☐ 45X/46XY   ☐ Otros:......................

Malformaciones cardíacas: ☐ no   ☐ sí
Tipo:
1 vávula aórtica tricúspide   5 CIV
2 coartación aorta   6 Ebstein
3 disección aorta   7 TGA
4 CIA   9 Otros

Edad del diagnóstico:

Malformaciones renales: ☐ no   ☐ sí
Tipo:
1 aplasia   4 agenesia unilateral
2 duplicación   9 Otros
3 herradura

Edad del dx:

Alteraciones autoimmunes: ☐ no ☐ sí
Tipo:
1 hipotiroidismo   4 artritis reumatoide juvenil
2 celiaquía   5 insuficiencia suprarrenal
3 enfermedad inflamatoria intestinal   9 otros:...............................

Edad del dx:

Intervenciones quirúrgicas: ☐ no ☐ sí
Comentarios:

Medicación actual: ☐ no ☐ sí
Comentarios:

Otras patologías: ☐ no ☐ sí
1 HTA   4 hipertrigliceridemia
2 hipertransaminasemia   5 intolerancia a la glucosa
3 hipercolesterolemia   9 otros:....................................

☐ Densitometría ósea: ☐ no ☐ sí

Fecha DMO inicial: Nº ID HCP:..........................
    Cadera: T-score: Z-score:
    Fémur: T-score: Z-score:
    Comentarios:

2.3. Antecedentes gineco-obstétricos:
Menarquia: Espontánea: ☐ no   ☐ sí

Tipo menstrual: ☐ Espontáneo   ☐ Inducido
    días duración: intervalo:

Hormona crecimiento(GH):   ☐ no   ☐ sí
Edad inicio:
Dosis:
Años de tratamiento:

Terapia hormonal (THS):   ☐ no   ☐ sí
Edad inicio estrógenos:
Edad inicio progestágenos:
Dosis:
Tratamiento actual:

Anticoncepción hormonal: ☐ no   ☐ sí:...............................

Historia obstétrica:
Hijos: ☐ no   ☐ sí   Vaginales:.................... Cesáreas:.................
Abortos: ☐ no   ☐ sí
Tratamiento esterilidad: ☐ no
                         ☐ Inducción ovulación
                         ☐ FIV
                         ☐ Ovodonación

2.4. Antecentes familiares:

0 No	5 intolerancia a la glucosa
1 HTA	6 alteraciones genitales
2 hipertransaminasemia	7 hipotiroidismo
3 hipercolesterolemia	8 autoimmunidad:....................
4 hipertrigliceridemia	9 otros:...................................

2. <u>Exploración física</u>

Peso: Talla: Perímetro abdominal:

Tensión arterial (mmHg):

Estadíos de Tanner (1-5):   B:

                                P:

Fenotipo:

0 Normal
1 epicantus
2 ptosis ocular
3 estrabismo
4 deformidad pabellón auricular
5 cuello corto
6 pterigium colli

7 escoliosis
8 implantación baja del pelo
9 linfedema EE
10 4º MC corto
11 cubitus valgus
12 genu valgum
99 Otros

Neurología:
Sincinesias:
0 no
1 en espejo

2 punta-dedo
3 pronosupinación

Disfunción cerebelosa:
0 no
1 Romberg

2 dismetría
3 Barany

Nistagmus espontáneo: ☐ no   ☐ sí
Retraso mental: ☐ no   ☐ sí

Otros: ....

FULL DE RECOLLIDA DE DADES D'OTORRINOLARINGOLOGIA

HIPOGONADISMES CONGÈNITS: PROTOCOL CLÍNIC ORL

Codi: ....
Data exploració: ....

RECOLLIDA DADES OTORRINOLÒGIQUES

1. TIPUS HIPOGONADISME:
☐ 0 Control (no exposat)
☐ 1 Sd Turner
☐ 2 Sd Kallmann
☐ 3 Disgenèsia gonadal pura 46XX
☐ 4 Disgenèsia gonadal pura 46XY

2. ANAMNESI:

2.1. Antecedents PERSONALS de patologia rinosinusal i anòsmia:
☐ no ☐ sí

☐ Traumatisme craneoencefàlic
☐ Rinitis al·lèrgica
☐ Rinosinusitis crònica sense poliposi
☐ Rinosinusitis crònica + poliposi nasal
☐ Asma bronquial
☐ Exposició a tòxics
☐ Anòsmia postviral
☐ Intervencions quirúrgiques (tipus+data):......................................
☐ Altres:...

Tabaquisme (☐ No ☐ Sí ☐ Ex-fumador/a)
☐ Altres:...

2.2 Antecedents PERSONALS de patologia auditiva: ☐ no
☐ sí

☐ Otitis externa aguda: ☐ D   ☐ E   ☐ bilateral
☐ Otitis externa crònica: ☐ D   ☐ E   ☐ bilateral
☐ Otitis mitjana: ☐ D   ☐ E   ☐ bilateral
☐ Drenatges timpànics: ☐ D   ☐ E   ☐ bilateral
☐ Altres:..

2.2 Antecedents FAMILIARS patologia ORL: ☐ no ☐ sí
☐ Hipòsmia / Anòsmia
☐ Rinitis al.lèrgica
☐ Rinosinusitis crònica amb/sense pòlips
☐ Asma bronquial
☐ Hipoacúsia
☐ Altres:..

3. EXPLORACIÓ ORL:

3.1   SEMIOLOGIA NASAL:

Escala EVA per a valorar la gravetat del símptoma (0= gens; 10= màxim):

3.1 Obstrucció Nasal 0 _____ 10

3.2 Hidrorrea / Rinorrea 0 _____ 10

3.3 Esternuts 0 _____ 10

3.4 Pruïja Nasal: 0 _____ 10

3.5 Pèrdua de l'olfacte 0 _____ 10

3.6 Pressió/dolor facial 0 _____ 10

3.2   ENDOSCÒPIA NASAL:

3.2.1. **Mucosa nasal**: ☐ normal ☐ hiperèmica ☐ edematosa

3.2.2. **Cornets hipertròfics:**   F.N. **Dreta** ☐ no ☐ sí
                                    F.N. **Esquerra** ☐ no ☐ sí

3.2.3. **Anomalies septals**:
Dreta   ☐ no   ☐ desviament   ☐ espina nasal
Esquerra   ☐ no   ☐ desviament   ☐ espina nasal

3.2.4. **Pòlips Nasals**:
Dreta   ☐ no   ☐ sí   Lildholdt   **D**: 0 1 2 3
Esquerra   ☐ no   ☐ sí   **E**: 0 1 2 3

3.2.5. **Secrecions purulentes a meat mig:**

Dreta   ☐ no   ☐ sí
Esquerra ☐ no   ☐ sí

Comentaris exploració nasal:..
....
....
....

3.3.   CAVITAT ORAL:

☐ Normal
☐ Agenèsia dental
☐ Fenedura labial
☐ Fenedura palatina
☐ Paladar ogival
☐ Micrognàtia
☐ Altres..

3.4.   OÏDA:

3.4.1. **Conducte auditiu extern:**

O.D.   ☐ normal   ☐ patològic:...................................
O.E.   ☐ normal   ☐ patològic:...................................

3.4.2. **Membrana timpànica:**

O.D.   ☐ normal   ☐ patològica:.................................
O.E.   ☐ normal   ☐ patològica:.................................

Comentaris exploració òtica:..
....
....
....

TEST D'OLFACTOMETRIA-GUSTOMETRIA BAST-24

Olfactometria

Nom del pacient: NHC:

Data:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		21	22	23	24
Detecció																									
Intensitat																									
Irritació																									
Frescura																									
Agradable																									
Definició																									
Coneixement																									
Identificació																									
Encert																									

I Par craneal	DT	DF	CO	ID	AC		V Par craneal	DT	DF	CO	ID	AC
	0	0	0	0	0			0	0	0	0	0

I PAR CRANEAL

V PAR CRANEAL

Gustometria

		D	S	AC	AM
Amargant	AM				1
Àcid	AC			1	
Salat	S		1		
Dolç	D	1			

Gust	
D	1
S	1
AC	1
AM	1
	4

GUSTO V-VII-IX-X
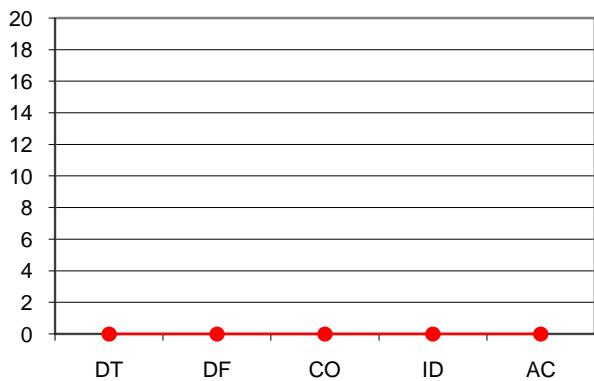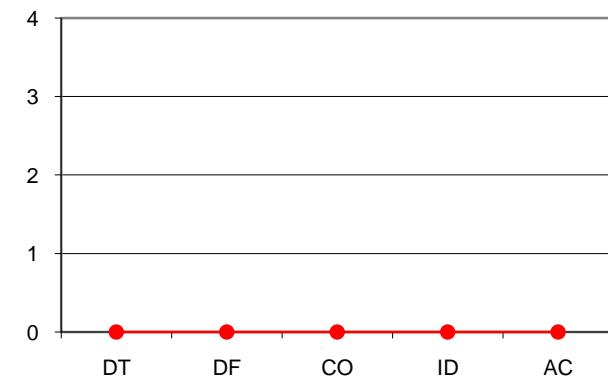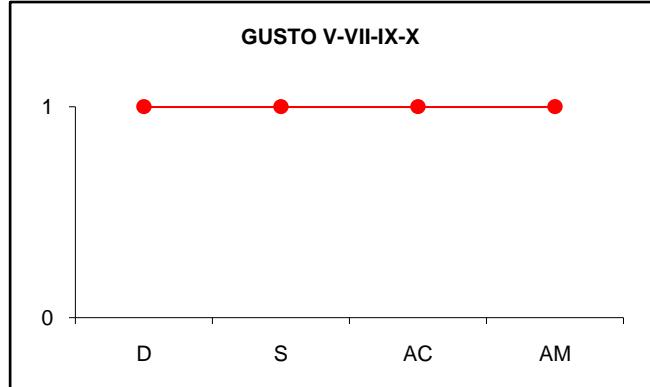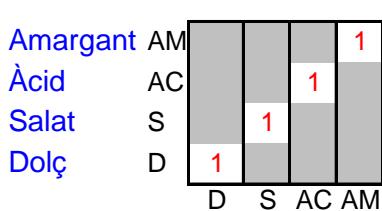
Resposta de les olors

1		2		3		4		5		1	
PINYA		*PLÀTAN*		*CEBA*		*A.AMARGA*		*CIRERA*		*VINAGRE*	
BOLET		*FORMATGE*		*MANDARINA*		*VAINILLA*	▓	*MADUIXA*		*AMONIAC*	
ANÍS	▓	*BAFS*		*CLAU*		*ROSA*		*FUMAT*	▓	*FORMOL*	▓
MELÓ		*COCO*	▓	*LLIMONA*	▓	*AIGUARRÀS*		*LLIMONA*		*MOSTASSA*	

6		7		8		9		10		2	
COCO		*ROSA*		*FORMAT*		*ANÍS*		*ANÍS*		*MOSTASSA*	
LLIMONA		*CEBA*		*BOLET*		*PLÀTAN*		*MADUIXA*		*VINAGRE*	▓
MELÓ	▓	*PINYA*		*CLAU*		*A.AMAR*	▓	*COCO*		*FORMOL*	
VAINILLA		*PLÀTAN*	▓	*MANDAR*	▓	*MANDARINA*		*GASOLINA*	▓	*AMONIAC*	

11		12		13		14		15		3	
PINYA	▓	*FORMATGE*	▓	*ROSA*		*LLIMONA*		*CIRERA*		*AMONIAC*	▓
PLÀTAN		*AIGUARRÀS*		*PINYA*		*A.AMAR*		*MADUIXA*	▓	*FORMOL*	
LLIMONA		*CLAU*		*CEBA*	▓	*ROSA*	▓	*ANÍS*		*VINAGRE*	
VAINILLA		*MANDAR*		*FORMAT*		*ANÍS*		*MELÓ*		*MOSTASSA*	

16		17		18		19		20		4	
AIGUARRÀS		*BAFS*	▓	*CEBA*		*ROSA*		*ANÍS*		*FORMOL*	
BOLET	▓	*FUMAT*		*CLAU*	▓	*VAINILLA*		*MELÓ*		*MOSTASSA*	▓
MELÓ		*PRÉSSEC*		*MANDARINA*		*AIGUARRÀS*	▓	*MADUIXA*		*AMONIAC*	
COCO		*GASOLINA*		*VAINILLA*		*PLÀTAN*		*PRÉSSEC*	▓	*VINAGRE*	

PRIMER PARELL CRANIAL (N OLFATORI)

Capacitat de detecció	**0** %
Capacitat de definició	0 %
Capacitat de recordar	0 %
Capacitat d'identificació espontània	0 %
Encerts correctes	**0** %
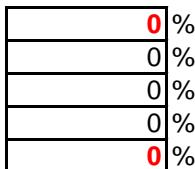
CINQUÉ PARELL CRANIAL (N TRIGÈMIN)

Capacitat de detecció	0 %
Capacitat de definició	**0** %
Capacitat de recordar	0 %
Capacitat d'identificació espontània	0 %
Encerts correctes	**0** %
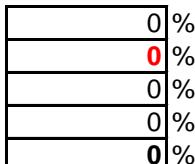
GUSTOMETRIA QUÍMICA   100 %

Comentaris

Orientació diagnòstica

QÜESTIONARI DE QUALITAT DE VIDA SF-36

CUESTIONARIO DE SALUD SF-36

VERSIÓN ESPAÑOLA 1.4 (junio de 1999)

INSTRUCCIONES:

Las preguntas que siguen se refieren a lo que usted piensa sobre su salud. Sus respuestas permitirán saber cómo se encuentra usted y hasta qué punto es capaz de hacer sus actividades habituales

Conteste cada pregunta tal como se indica. Si no está seguro/a de cómo responder a una pregunta, por favor conteste lo que le parezca más cierto.

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1. En general, usted diría que su salud es:

    1 ☐ Excelente

    2 ☐ Muy buena

    3 ☐ Buena

    4 ☐ Regular

    5 ☐ Mala

2. ¿Cómo diría que es su salud actual, <u>comparada con la de hace un año</u>?

    1 ☐ Mucho mejor ahora que hace un año

    2 ☐ Algo mejor ahora que hace un año

    3 ☐ Más o menos igual que hace un año

    4 ☐ Algo peor ahora que hace un año

    5 ☐ Mucho peor ahora que hace un año

LAS SIGUIENTES PREGUNTAS SE REFIEREN A ACTIVIDADES O COSAS QUE USTED PODRÍA HACER EN UN DÍA NORMAL.

3. Su salud actual, ¿le limita para hacer **esfuerzos intensos**, tales como correr, levantar objetos pesados, o participar en deportes agotadores?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

4. Su salud actual, ¿le limita para hacer **esfuerzos moderados**, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de una hora?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

5. Su salud actual, ¿le limita para **coger o llevar la bolsa de la compra?**

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

6. Su salud actual, ¿le limita para **subir varios pisos** por la escalera?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

7. Su salud actual, ¿le limita para **subir un solo piso** por la escalera?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

8. Su salud actual, ¿le limita para **agacharse o arrodillarse?**

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

9. Su salud actual, ¿le limita para caminar **un kilómetro o más**?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

10. Su salud actual, ¿le limita para caminar **varias manzanas** (varios centenares de metros)?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

11. Su salud actual, ¿le limita para caminar **una sola manzana** (unos 100 metros)?

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

12. Su salud actual, ¿le limita para **bañarse o vestirse por sí mismo?**

    1 ☐ Sí, me limita mucho

    2 ☐ Sí, me limita un poco

    3 ☐ No, no me limita nada

LAS SIGUIENTES PREGUNTAS SE REFIEREN A PROBLEMAS
EN SU TRABAJO O EN SUS ACTIVIDADES COTIDIANAS.

13. Durante las 4 últimas semanas, ¿tuvo que **reducir el tiempo** dedicado al trabajo o a sus actividades cotidianas, a causa de su salud física?

    1 ☐ Sí

    2 ☐ No

14. Durante las 4 últimas semanas, ¿**hizo menos** de lo que hubiera querido hacer, a causa de su salud física?

    1 ☐ Sí

    2 ☐ No

15. Durante las 4 últimas semanas, ¿tuvo que **dejar de hacer algunas tareas** en su trabajo o en sus actividades cotidianas, a causa de su salud física?

    1 ☐ Sí

    2 ☐ No

16. Durante las 4 últimas semanas, ¿tuvo **dificultad** para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal), a causa de su salud física?

    1 ☐ Sí

    2 ☐ No

17. Durante las 4 últimas semanas, ¿tuvo que **reducir el tiempo** dedicado al trabajo o a sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido, o nervioso?

    1 ☐ Sí

    2 ☐ No

18. Durante las 4 últimas semanas, ¿**hizo menos** de lo que hubiera querido hacer, a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?

    1 ☐ Sí

    2 ☐ No

19. Durante las 4 últimas semanas, ¿no hizo su trabajo o sus actividades cotidianas tan **cuidadosamente** como de costumbre, a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?

    1 ☐ Sí

    2 ☐ No

20. Durante las 4 últimas semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas?

    1 ☐ Nada

    2 ☐ Un poco

    3 ☐ Regular

    4 ☐ Bastante

    5 ☐ Mucho

21. ¿Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas?

1 ☐ No, ninguno

2 ☐ Sí, muy poco

3 ☐ Sí, un poco

4 ☐ Sí, moderado

5 ☐ Sí, mucho

6 ☐ Sí, muchísimo

22. Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?

1 ☐ Nada

2 ☐ Un poco

3 ☐ Regular

4 ☐ Bastante

5 ☐ Mucho

LAS PREGUNTAS QUE SIGUEN SE REFIEREN A CÓMO SE HA SENTIDO Y CÓMO LE HAN IDO LAS COSAS DURANTE LAS 4 ÚLTIMAS SEMANAS. EN CADA PREGUNTA RESPONDA LO QUE SE PAREZCA MÁS A CÓMO SE HA SENTIDO USTED.

23. Durante las 4 últimas semanas, ¿cuánto tiempo se sintió lleno de vitalidad?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Muchas veces

4 ☐ Algunas veces

5 ☐ Sólo alguna vez

6 ☐ Nunca

24. Durante las 4 últimas semanas, ¿cuánto tiempo estuvo muy nervioso?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Muchas veces

4 ☐ Algunas veces

5 ☐ Sólo alguna vez

6 ☐ Nunca

25. Durante las 4 últimas semanas, ¿cuánto tiempo se sintió tan bajo de moral que nada podía animarle?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Muchas veces

4 ☐ Algunas veces

5 ☐ Sólo alguna vez

6 ☐ Nunca

26. Durante las 4 últimas semanas, ¿cuánto tiempo se sintió calmado y tranquilo?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Muchas veces

4 ☐ Algunas veces

5 ☐ Sólo alguna vez

6 ☐ Nunca

27. Durante las <u>4 últimas semanas</u>, ¿cuánto tiempo tuvo mucha energía?

    1 ☐ Siempre

    2 ☐ Casi siempre

    3 ☐ Muchas veces

    4 ☐ Algunas veces

    5 ☐ Sólo alguna vez

    6 ☐ Nunca

28. Durante las <u>4 últimas semanas</u>, ¿cuánto tiempo se sintió desanimado y triste?

    1 ☐ Siempre

    2 ☐ Casi siempre

    3 ☐ Muchas veces

    4 ☐ Algunas veces

    5 ☐ Sólo alguna vez

    6 ☐ Nunca

29. Durante las <u>4 últimas semanas</u>, ¿ cuánto tiempo se sintió agotado?

    1 ☐ Siempre

    2 ☐ Casi siempre

    3 ☐ Muchas veces

    4 ☐ Algunas veces

    5 ☐ Sólo alguna vez

    6 ☐ Nunca

30. Durante las <u>4 últimas semanas</u>, ¿ cuánto tiempo se sintió feliz?

    1 ☐ Siempre

    2 ☐ Casi siempre

    3 ☐ Muchas veces

    4 ☐ Algunas veces

    5 ☐ Sólo alguna vez

    6 ☐ Nunca

31. Durante las <u>4 últimas semanas</u>, ¿ cuánto tiempo se sintió cansado?

    1 ☐ Siempre

    2 ☐ Casi siempre

    3 ☐ Muchas veces

    4 ☐ Algunas veces

    5 ☐ Sólo alguna vez

    6 ☐ Nunca

32. Durante las <u>4 últimas semanas</u>, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)?

    1 ☐ Siempre

    2 ☐ Casi siempre

    3 ☐ Algunas veces

    4 ☐ Sólo alguna vez

    5 ☐ Nunca

POR FAVOR, DIGA SI LE PARECE <u>CIERTA O FALSA</u>
CADA UNA DE LAS SIGUIENTES FRASES.

33. Creo que me pongo enfermo más fácilmente que otras personas.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

34. Estoy tan sano como cualquiera.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

35. Creo que mi salud va a empeorar.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

36. Mi salud es excelente.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

QÜESTIONARI DE SEXUALITAT FSFI

Código: **Fecha:**

<u>Test de sexualidad FSFI</u>

Este cuestionario ha sido diseñado para mujeres que experimentan poco deseo sexual y les preocupa. En este cuestionario se le preguntará sobre sus sentimientos entorno a la sexualidad, su actividad sexual y sobre algunas preocupaciones que pueda haber tenido sobre su grado de interés en el sexo durante las últimas 4 semanas. Lea atentamente cada frase y marque con una cruz la casilla que mejor se corresponda con su experiencia durante las <u>*últimas 4 semanas.*</u>

1.-Durante las últimas 4 semana, con qué frecuencia ha sentido deseo o interés sexual.

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

2.-Durante las últimas 4 semanas, cómo cuantificaría su nivel de deseo o interés sexual.

☐ 5.-Muy alto

☐ 4.-Alto

☐ 3.-Moderado

☐ 2.-Bajo

☐ 1.-Muy bajo o nulo

3.- Durante las últimas 4 semanas, con qué frecuencia ha surgido su excitación sexual durante una relación sexual o actividad de tipo erótico.

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No he realizado ninguna actividad sexual

4.- Durante las últimas 4 semanas, cómo cuantificaría su nivel de excitación durante una relación sexual o actividad de tipo erótico.

☐ 5.-Muy alto

☐ 4.-Alto

☐ 3.-Moderado

☐ 2.-Bajo

☐ 1.-Muy bajo o nulo

☐ 0.-No he realizado ninguna actividad sexual

5.- Durante las últimas 4 semanas, qué nivel de confianza en sí misma ha sentido durante una relación sexual o actividad de tipo erótico.

☐ 5.-Confianza muy alta

☐ 4.-Confinaza alta

☐ 3.-Confianza moderada

☐ 2.-Confianza baja

☐ 1.-Confianza muy baja o nula

☐ 0.-No he realizado ninguna actividad sexual

6.- Durante las últimas 4 semanas, con qué frecuencia se ha sentido satisfecha con su excitación durante una relación sexual o actividad de tipo erótico.

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No he realizado ninguna actividad sexual

7.- Durante las últimas 4 semanas, con qué frecuencia ha notado su vagina lubricada/húmeda durante una relación sexual o actividad de tipo erótico

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No he realizado ninguna actividad sexual

8.- Durante las últimas 4 semanas, con qué dificultad ha conseguido notar su vagina lubricada/húmeda durante una relación sexual o actividad de tipo erótico.

☐ 5.- Sin dificultad

☐ 4.-Ligeramente difícil

☐ 3.-Difícil

☐ 2.-Muy difícil

☐ 1.-Imposible o extremadamente díficil

☐ 0.-No he realizado ninguna actividad sexual

9.-Durante las últimas 4 semanas, con qué frecuencia ha mantenido su vagina lubricada/húmeda hasta el final de la relación sexual o actividad de tipo erótico

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No he realizado ninguna actividad sexual

10.- Durante las últimas 4 semanas, con qué dificultad ha conseguido mantener su vagina lubricada/húmeda hasta el final de la relación sexual o actividad de tipo erótico.

☐ 5.- Sin dificultad

☐ 4.-Ligeramente difícil

☐ 3.-Difícil

☐ 2.-Muy difícil

☐ 1.-Imposible o extremadamente díficil

☐ 0.-No he realizado ninguna actividad sexual

11.-Durante las últimas 4 semanas, cuando ha tenido una relación sexual, con qué frecuencia ha llegado al orgasmo.

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No he realizado ninguna actividad sexual

12.- Durante las últimas 4 semanas, cuando ha tenido una relación sexual, cómo de difícil ha sido para usted llegar al orgasmo.

- ☐ 5.-Sin dificultad
- ☐ 4.-Ligeramente difícil
- ☐ 3.-Difícil
- ☐ 2.-Muy difícil
- ☐ 1.-Imposible o extremadamente difíficl
- ☐ 0.-No he realizado ninguna actividad sexual

13.- Durante las últimas 4 semanas, cómo de satisfecha se ha sentido con su capacidad de llegar al orgasmo durante una relación sexual o actividad de tipo erótico.

- ☐ 5.-Muy satisfecha
- ☐ 4.-Moderadamente satisfecha
- ☐ 3.-Igualmente de satisfecha que insatisfecha
- ☐ 2.-Moderadamente insatisfecha
- ☐ 1.-Muy insatisfecha
- ☐ 0.-No he realizado ninguna actividad sexual

14.- Durante las últimas 4 semanas, cómo de satisfecha se ha sentido con el vínculo emocional entre usted y su pareja, durante una relación sexual.

- ☐ 5.-Muy satisfecha
- ☐ 4.-Moderadamente satisfecha
- ☐ 3.-Igualmente de satisfecha que insatisfecha
- ☐ 2.-Moderadamente insatisfecha
- ☐ 1.-Muy insatisfecha
- ☐ 0.-No he realizado ninguna actividad sexual

15.-Durante las última 4 semanas, cómo de satisfecha se ha sentido con su relación a nivel sexual con su pareja.

- ☐ 5.-Muy satisfecha
- ☐ 4.-Moderadamente satisfecha
- ☐ 3.-Igualmente de satisfecha que insatisfecha
- ☐ 2.-Moderadamente insatisfecha
- ☐ 1.-Muy insatisfecha
- ☐ 0.-No tengo pareja

16.-Durante las últimas 4 semanas, cómo de satisfecha se ha sentido con su vida sexual en general.

☐ 5.-Muy satisfecha

☐ 4.-Moderadamente satisfecha

☐ 3.-Igualmente de satisfecha que insatisfecha

☐ 2.-Moderadamente insatisfecha

☐ 1.-Muy insatisfecha

17.- Durante las últimas 4 semanas, con qué frecuencia ha experimentado dolor o malestar vaginal durante la penetración

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No ha habido ningún intento de penetración

18.- Durante las últimas 4 semanas, con qué frecuencia ha experimentado dolor o malestar vaginal después de la penetración.

☐ 5.-Siempre o casi siempre

☐ 4.-La mayoría de veces

☐ 3.-A veces

☐ 2.-Alguna vez

☐ 1.-Casi nunca o nunca

☐ 0.-No ha habido ningún intento de penetración

19.- Durante las últimas 4 semanas, cómo valoraría su nivel de malestar o dolor durante o después de la penetración vaginal.

☐ 5.-Muy alto

☐ 4.-Alto

☐ 3.-Moderado

☐ 2.-Bajo

☐ 1.-Muy bajo o nulo

☐ 0.- No ha habido ningún intento de penetración

Categoria	Preguntas	Puntuación	Factor	Puntuación corregida
Deseo	1 i 2	1-5	0.6	1.3-6.0
Excitación	3-6	0-5	0.3	0-6.0
Lubricación	7-10	0-5	0.3	0-6.0
Orgasmo	11-13	0-5	0.4	0-6.0
Satisfacción	14-16	0-5	0.4	0.8-6.0
Dolor y malestar	17-19	0-5	0.4	0-6.0
		Rango de la puntuación total	36.0	