

Dia 1

UMC St Radboud

Turner syndrome

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Section of endocrinology

UMC St Radboud
Turnerpolkliniek



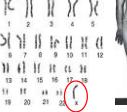
Dia 2

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Turner syndrome

1938
Henry Turner: description of clinical triad:-
- short stature
- 'sexual infantilism'
- dysmorphic abnormalities

1959
C.E. Ford: discovery of X chromosomal monosomy



4 APRIL 1959 ORIGINAL ARTICLES THE LANCET

A SEX-CHROMOSOME ANOMALY IN A CASE OF GONADAL DYSGENESIS TURNER'S SYNDROME

K. W. Jones Ph.D. Landau M.R.C. Medical Research Council Radiobiology Research Unit, AtOMIC RESEARCH ESTABLISHMENT, HARWELL, BERKSHIRE

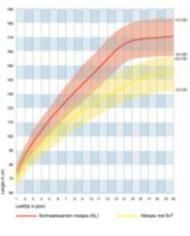
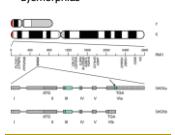
Dia 3

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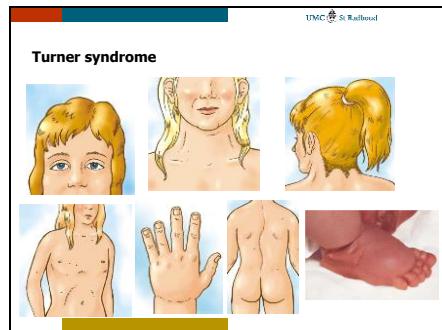
Turner syndrome

1:2500 live born girls

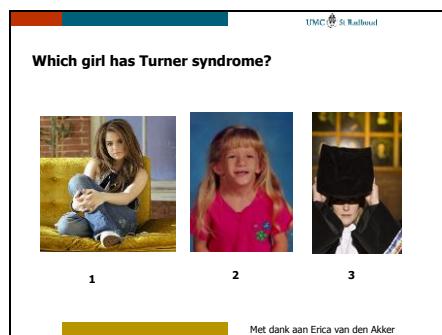
- short stature (mean 147 cm); growth hormone treatment results
- ovarian failure: induction of puberty
- dysmorphias



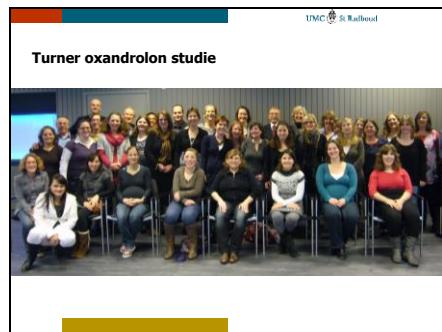
Dia 4



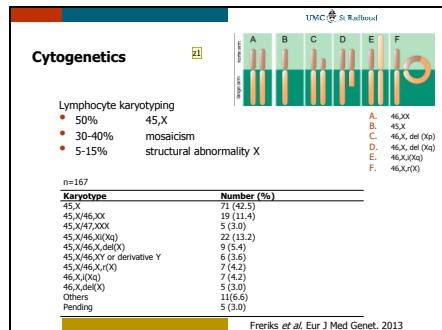
Dia 5



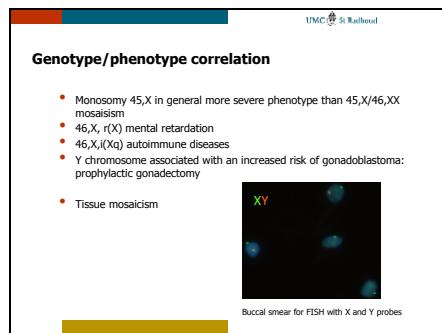
Dia 6



Dia 7



Dia 8



Dia 9

Wide range of morbidity

algemeen	genodermatose	0-100	skelt	vervormde hondelijfpijn	4%
	genodermatose, waardoor uit-	0-100		cubitus valgus	5%
	blijvende gehandicaptaking			achterhoekse of straal	5%
		0-100		graat valgus	3%
	chronische ontstekingsziekten			congenitale hemiplegie	2%
ogen	epicanthus	0-100		congenitale hemicamptie	1%
	exotropie	20		schaduwendeffecten	1%
	strabismus	15		afwijkingen van aanzicht	5%
oorm	otitis media	50	haut sono	afwijkingen	25-40%
	otitis media en doofheid	50		cochlearitis	10-14%
	oorschelpbeschijptingen	45		cochlear actueel	10-14%
mond	micrognathie	50		anorectale fistule	5-42%
	microtia	50		anorectale fistule en anorektomie	2%
	afleidende aangeboren handen en vingers	1	maag, darm, lever	diarrhoees	
nek	breuk halswervel	40		leveren en maagdrukkingen	3-40%
	breuk halswervel	40		hefbladder	10-15%
	breuk halswervel ('webbed neck')	25		hefbladder en strottekkens of	
	pregerug cell ('webbed neck')	25		uitstrekken	
schildklier	auto-immuunthyreoïdialiteit	25		uitstrekken	
darm	auto-immuunthyreoïdialiteit	15-50		uitstrekken	
huid, vingers, haai	innovatie van de spil	5	neuro-	stomatitis in visiel-spécifie	1%
	toegewijde rompeling	5	pathologische	stomatitis in visiel-spécifie	
	multifocale neurofibromatose	25	problemen	lengte, kleur, vorm, oppervlak	
	multiple pigmenteringen nervi	25	overig	lengtevermindering	
	ataxie	5		diabetes mellitus type 2	15-50%
	ataxie	5		hypertension	24-50%
	vitiligo	5			

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Freriks et al. NTVG 2007

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Cardiovascular morbidity

Life expectancy - 13 years / cardiovascular mortality x 3

Structural abnormalities heart / aorta

- congenital: bicuspid aortic valve (15-30%), aortic coarctation (10-15%)
- acquired: aortic dilation / aneurysm (25%) and dissection

1. normal aortic valve
2. bicuspid aortic valve
3. aortic coarctation

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Cardiovascular morbidity

Increased risk of atherosclerosis

- hypertension
 - ✓ 50% of young adults
 - ✓ chance of dissection in case of aortic dilation / bicuspid aortic valve (treatment goal SBP <120 mmHg)
- diabetes mellitus type 1 x11, type 2 x3.5
- dyslipidemia 40-50% of young adults

4. aortic dilation / aneurysm

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Osteoporosis and fractures

osteopenia, osteoporosis (50%)*

- intrinsic defect in cortical bone maturation
- trabecular bone loss due to estrogen deficiency

higher tendency to fall

- compromised motor skills

fracture risk 2-3x

*DEXA underestimates BMD in short stature

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Auto-immune disorders

- Hypothyroidism in 25-40% <40 years (vs 2% in general population)
- Celiac disease in 5% (vs 1% in general population)
- Most prevalent in X,isoXq karyotype



Autoantibody	Positive serology	Autoantibody with disease
Anti-TPO ($n = 106$)	45% (48/106)	33% (16/48) had hypothyroidism 4% (2/48) had hyperthyroidism
CD antibody ($n = 106$)	18% (19/106)	11% (2/19) had known CD 16% (3/19) received the CD diagnosis
Anti-GAD-65 ($n = 106$)	4% (4/106)	50% (2/4) classified as type 2 diabetes
Adrenocortical autoantibody ($n = 107$)	1% (1/107)	None

Mortensen et al. Clin Exp Immunol 2009

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Estrogen deficiency and infertility

Hormone replacement therapy

- Ovarian failure: estradiol/dydrogesterone, biphasic or continuous
- Anticonception: (46,XX mosaicism and menstrual cycle); ethynodiolestradiol/levonorgestrel



Fertility

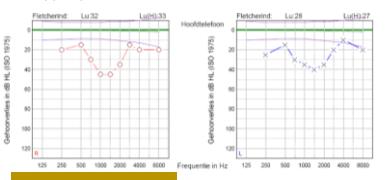
- 2-6% 'spontaneous' pregnancy (46,XX mosaicism)
- Reproductive techniques
 - IVF after egg donation
 - Egg preservation from mother / sister
 - Experimental: egg preservation during childhood
- Higher risk of abortion, eclampsia, premature birth, growth retardation, aortic dissection (2%)

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Ear and hearing problems

- Structural abnormalities external and internal ear
- Conductive loss due to recurrent otitis media during childhood
- Early presbycusis



Dia 16

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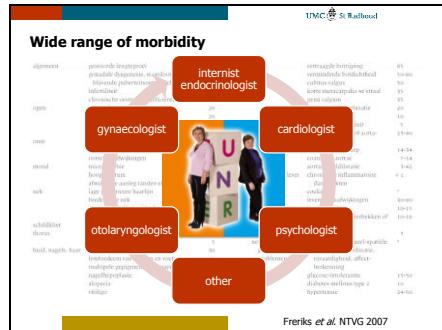
Dia 17

IMC St. Gallen

Dia 18

Wide range of morbidity		HMC St Radboud			
algemeen	genoemde langperiode	0-5-500	slieker	vermoedige herontstijging	85
	genoemde dyspareunie, waardoor uitgaande potentiële gezondheid			vermoedende herontstijging	50-85
	intimafouten			hoede saligheid	35
	chronische overproduktiefaciliteit	0-5-50		hoede stigmatisering en stress	35
ogen	chromofobie	0-5-50		geen valgallen	35
	homofobie	0-5-50		vergrijzing	35
	bijzonderheid	20		weesleven	10
	stratificatie	15		maatschappelijk familie	10
	prostitutie	15	harm-auma	complexe kwestie van 'art-ta'	25-40
oorme	otitis media	20		afleidingskunst	10
	slakkensoorten of doosvliezen	20		herontstijging	14-34
	onrechthoofdgebijten	15		concreet avastar	7-14
mond	misnietgeur	50		vergrijzing	4-12
	hoge gebit	50	mang, dure, leeuw	vergrijzing en informatie	
	afleidende aantrek rondom en kleuren	1		democratieken	
nek	hoge hals	1		tevredenheid	7
	lage hals	1		levenseconomieën	7
	hoede korte nek	40		veroudering en maatschappijen	10-30
	progeria	25		dagelijks leven en steekbedrijf	10-15
	relatieve veroudering	25		steekbedrijf	10-15
schildklier	auto-immuunthyreose	15-50	x		
thorax	haut-thyreoïdeopathie	15-50	x		
	invoering van de tepel	15-50	x		
	topografische rompeling	15-50	x		
	veroudering en verouderen op wezen	15-50	x		
	multiple pigmenterende naevi	25	x		
	magneetgevoeligheid	10	overig		
	alopécie	5			
huid, vingers, hair	vitiligo	5			
				dialites mellitus type 1	10-30
				hypersensitie	24-30

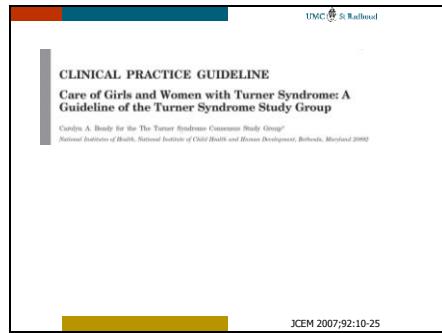
Dia 19



Dia 20



Dia 21



Dia 22

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Turner clinics for adult patients

Consultations

- endocrinologist
- gynecologist
- cardiologist
- ENT physician
- (psychologist)

Investigations

- lab investigations
- cardiac ultrasound
- MRI aorta
- audiogram
- DEXA

Multidisciplinary meetings

The map shows the locations of several Dutch medical centers: UMC St Radboud (in Nijmegen), VUMC (in Amsterdam), UMCN (in Groningen), and Erasmus MC (in Rotterdam). Other smaller dots represent additional clinics or centers.

Dia 23

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Klinische Richtlijn Turner Syndroom

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Nederlandse Wijsmuller Multidisciplinary Network Turner Syndromen
Onderste 2010

Dia 24

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Turnerpolykliniek

periodieke labscreening

bij diagnose	tot 18 jaar	vrouwussen baseline	vrouwussen follow-up
TSH	x (>4 jaar)	1x/jaar	1x/1-2 jaar
coeliakiescrewing	x	1x/3-5 jaar	1x/3-5 jaar
ASAT	x (>10 jaar)	1x/3-5 jaar	1x/2-3 jaar
glucose	x (>10 jaar)	1x/3-5 jaar va pubertet	1x/1-2 jaar
HbA1c	x (>10 jaar)	1x/3-5 jaar va pubertet	1x/1-2 jaar
LCHC	x (>10 jaar)	1x/3-5 jaar va pubertet	1x/1-2 jaar
FSH	x (>10 jaar)	1x/jaar bij laag FSH	op indicatie
AMH	x (>10 jaar)	1x/jaar bij laag FSH	op indicatie

Klinische Richtlijn Turner Syndroom

Dia 25

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ORIGINAL ARTICLE
Endocrine Care

Standardized Multidisciplinary Evaluation Yields Significant Previously Undiagnosed Morbidity in Adult Women with Turner Syndrome

Kim Freriks, Sonja E. Timmermans, California C. M. Beemer-Sok, Chin M. van der Velde, Renata T. Nederhof-Meier, Bartje J. Omen-Dijk, D. M. Braat, Dominique F. C. M. Smeets, Dick H. P. M. Kunst, Ad R. M. M. Hermus, and Henk J. L. M. Timmers

Departments of Endocrinology (K.F., R.T.M.M., A.R.M.H., H.J.L.M.T.), Cardiology (J.T.), Obstetrics and Gynecology (D.M.B.), Pathology (C.M.V.), Pediatric Endocrinology (B.J.O.), Human Genetics (G.F.C.M.S.), and Oncology (D.H.P.M.K.) Radboud University Nijmegen Medical Center, 6525 HB Nijmegen, The Netherlands

Freriks et al. JCEM 2011

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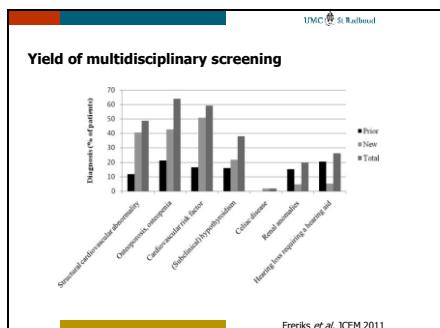
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TABLE 4. TS-associated morbidity ($n = 150$)

Previous diseases (n)	Changes in treatment (n)	New diagnosis (n)	Observed frequency (%)	Frequency literature (%)
Bicuspid aortic valve	12	0	10 ^a	15–31
Aortic coarctation	2	0	6 ^a	7–14
Bicuspid aortic coarctation	3	0	4 ^a	—
Elongation of the transverse aortic arch	0	0	27 ^a	18 ^a
Diabetes mellitus	4 ^b	0	34 ^a	3–42
Diabetes type 1	2 ^c	0	0 ^a	1 ^c
Diabetes type 2	2 ^c	0	0 ^a	3–75 ^c
Glucose intolerance	2 ^c	0	12 ^a	7–50 ^c
Hypertension	17 ^c	0	39 ^a	2–45 ^c
Dyslipidemia	8	0	52 ^a	40 ^a
Osteoporosis	10 ^c	0	8 ^a	12 ^c
Osteopenia	22 ^c	0	56 ^a	20–70 ^c
Osteoporosis or osteopenia	32 ^c	4	64 ^a	50–80 ^c
Hepatic steatosis	17 ^c	0	13 ^a	1–80 ^c
Subclinical hypothyroidism	7	2	37 ^a	27 ^a
Celiac disease	0	0	3 ^a	4–6 ^a
Renal anomalies	23 ^d	0	7 ^a	28–38 ^d
Liver enzyme disturbances	5	0	49 ^a	33–80 ^a
Immunodeficiencies and/or infections	31	1 ^e	30 ^a	21–54 ^a

Freriks et al. JCEM 2011

Dia 27



Dia 28

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Conclusions

- Besides short stature and ovarian failure, patients with Turner syndrome are prone to a wide range of morbidity throughout life with a large phenotypic variation
- This requires multidisciplinary care with standardized screening and careful transition from pediatric into adult medical care
