Organ Pathophysiology
The Human Model

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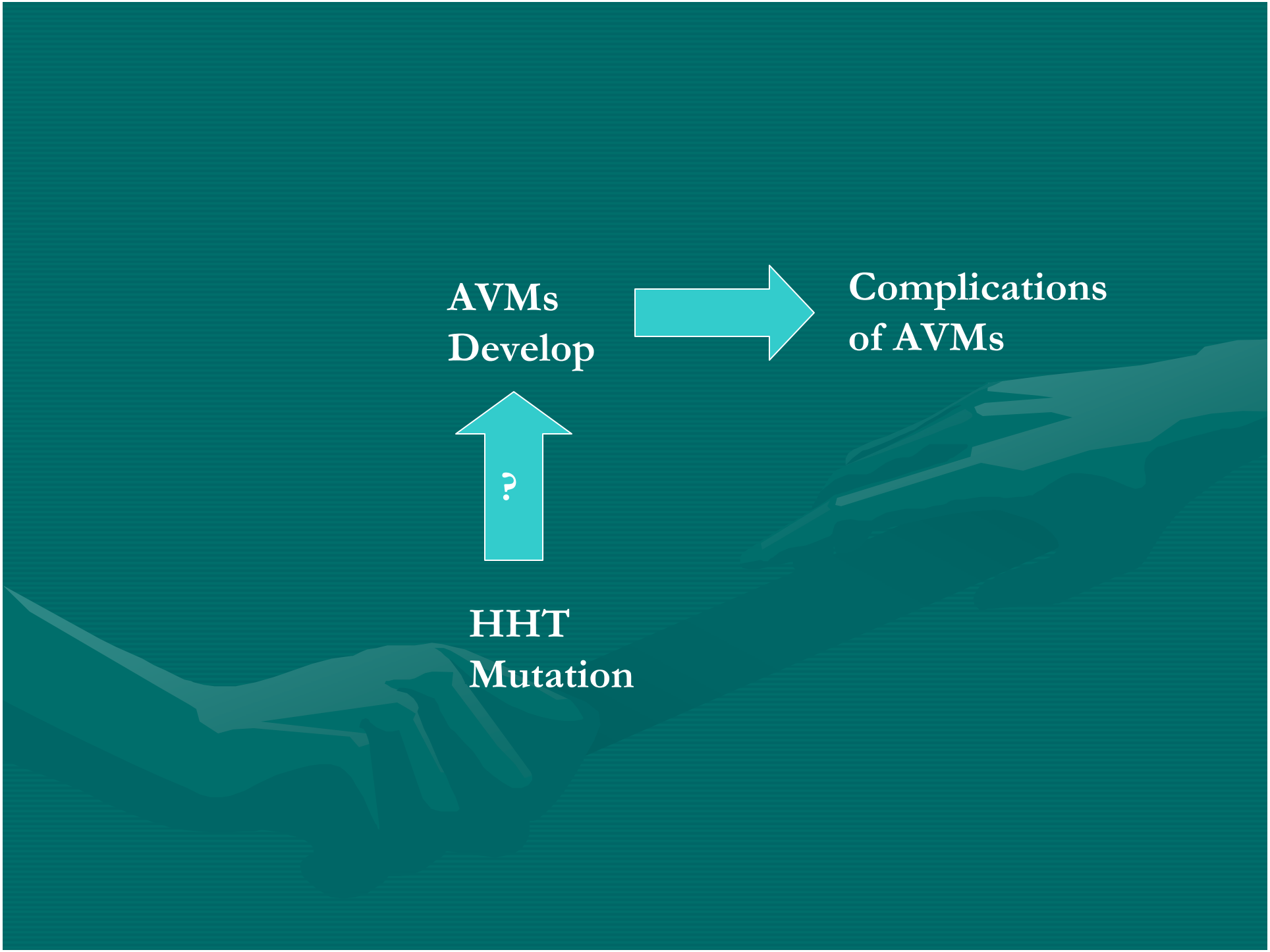
Outline

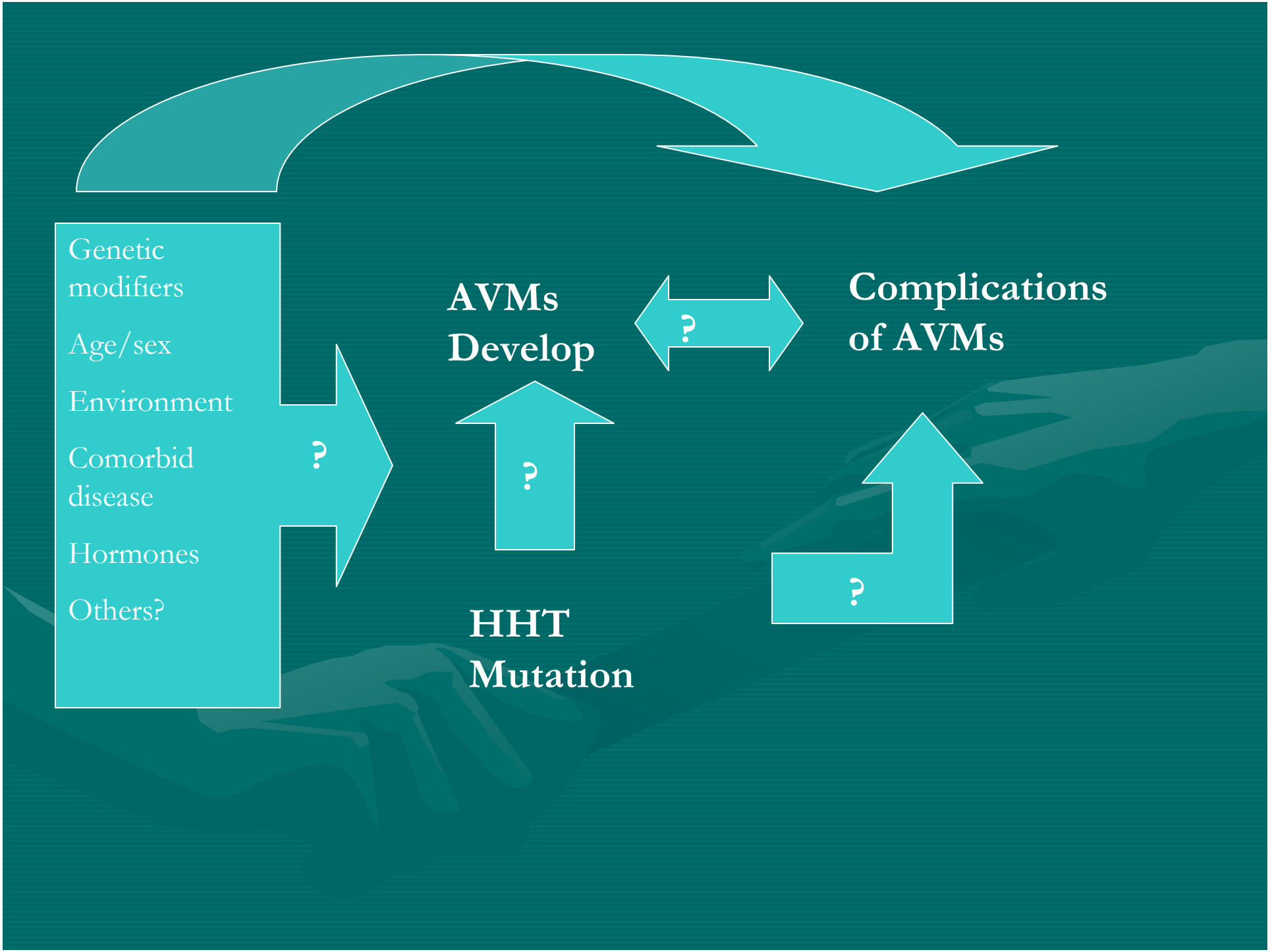
- Clinical Presentation
- Genotype-Phenotype Correlation
- Heterogeneity of clinical presentation
- Factors affecting disease progression/severity
- Mechanistic research in humans
- Medical Therapies in humans

Clinical Presentation

- Fragile vessels: Bleeding
  - Mucosal telangiectasia
  - Visceral arteriovenous malformations (AVMs)
- A-V connections: Complication of Shunting
  - Visceral AVMs
  - Visceral telangiectasia (diffuse)
- Pathology of the telangiectasia
  - Dilated arteriole connected to dilated venule, with excessive smooth muscle layers with perivascular lymphocytes

Jacobson et al Am J Path 2000


AVMs
Develop
Complications
of AVMs
?
HHT
Mutation


Genetic modifiers
Age/sex
Environment
Comorbid disease
Hormones
Others?
?
AVMs Develop
?
HHT Mutation
?
Complications of AVMs
?

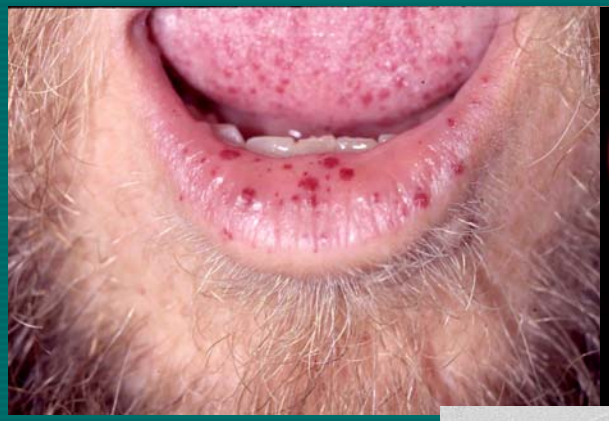
Typical HHT Patient

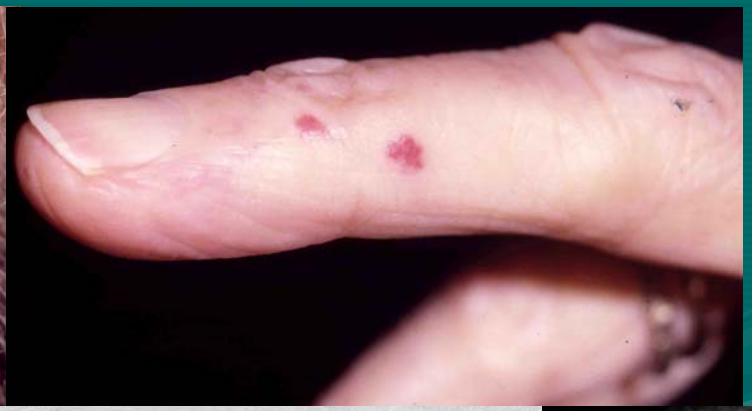
- 40 years old, female
- Daily epistaxis, 10-15min, heavy flow
- 5 telangiectasias
- Iron deficiency, mild anemia
- Otherwise asymptomatic but…

Potential Organ Involvement

- Cerebral AVMs: 5-10%
- Pulmonary AVMs: 30%
- Liver VMs: 50-70%
- GI telangiectasia: 50%
- Spinal AVMs <1%

AV Malformations



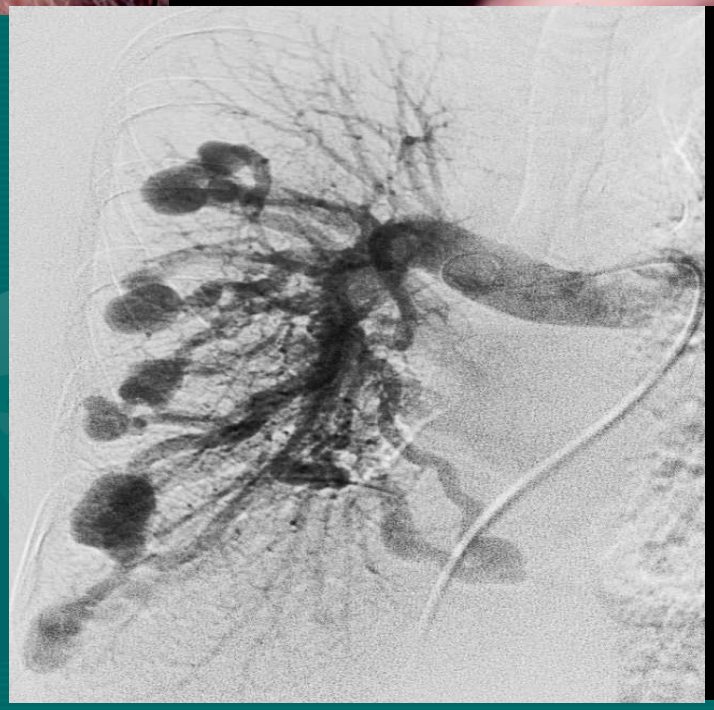


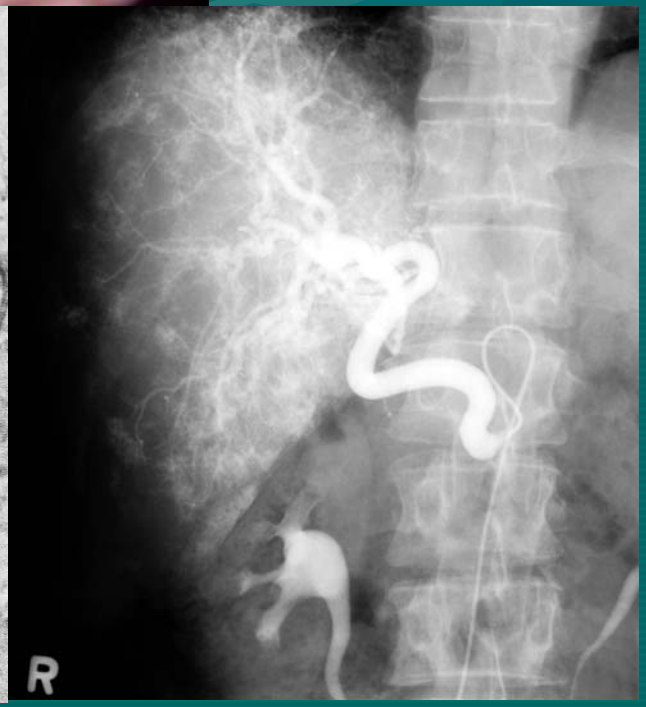
Prevalence

1/5000

Clinical Diagnosis:

1. Epistaxis
2. Telangiectasia
3. Visceral AVMs
4. Family History





Less Affected Areas/Organs

- Spine
- Larynx>Tracheobronchial tree
- Bronchial vasculature
- Pancreas
- Kidney
- Bladder
- Uterus?
- Limbs

Potential Complications

Cerebral AVMs	5-10%	➢ Stroke, seizures, death
PAVMs	30%	➢ Massive hemoptysis, hemothorax, stroke, cerebral abscess, death
LVMs	50-70%	➢ Heart failure, portal hypertension, death

More Potential Complications

GI telangiectasia		➢ GI bleeding, severe anemia, transfusion dependence, death
Spinal AVMs	<1%	➢ paralysis

HHT Morbidity

"Pendant les **trois (3)** premiers jours, je me suis borné à faire du **tamponnement** local avec de l'ouate et de la **vaseline**, tandis que le malade prenait du **fer**, de l'eau de Robel et de l'**opium**….les epistaxis ont continué de plus belle"

H. Rendu 1896

HHT and Life Expectancy

- Median age at death in parents of HHT patients:
  - HHT parent: 63 yrs
  - Non-HHT: 70 yrs
- HHT parents' Mortality ($P<0.05$) (N=40):
  - Early peak <50 yrs
  - Second peak 60-79 yrs
- Factors influencing Life expectancy:
  - HHT diagnosis for age>30
  - No association with sex, ALK1, Endoglin

Sabba C et al. QJM 2006 May

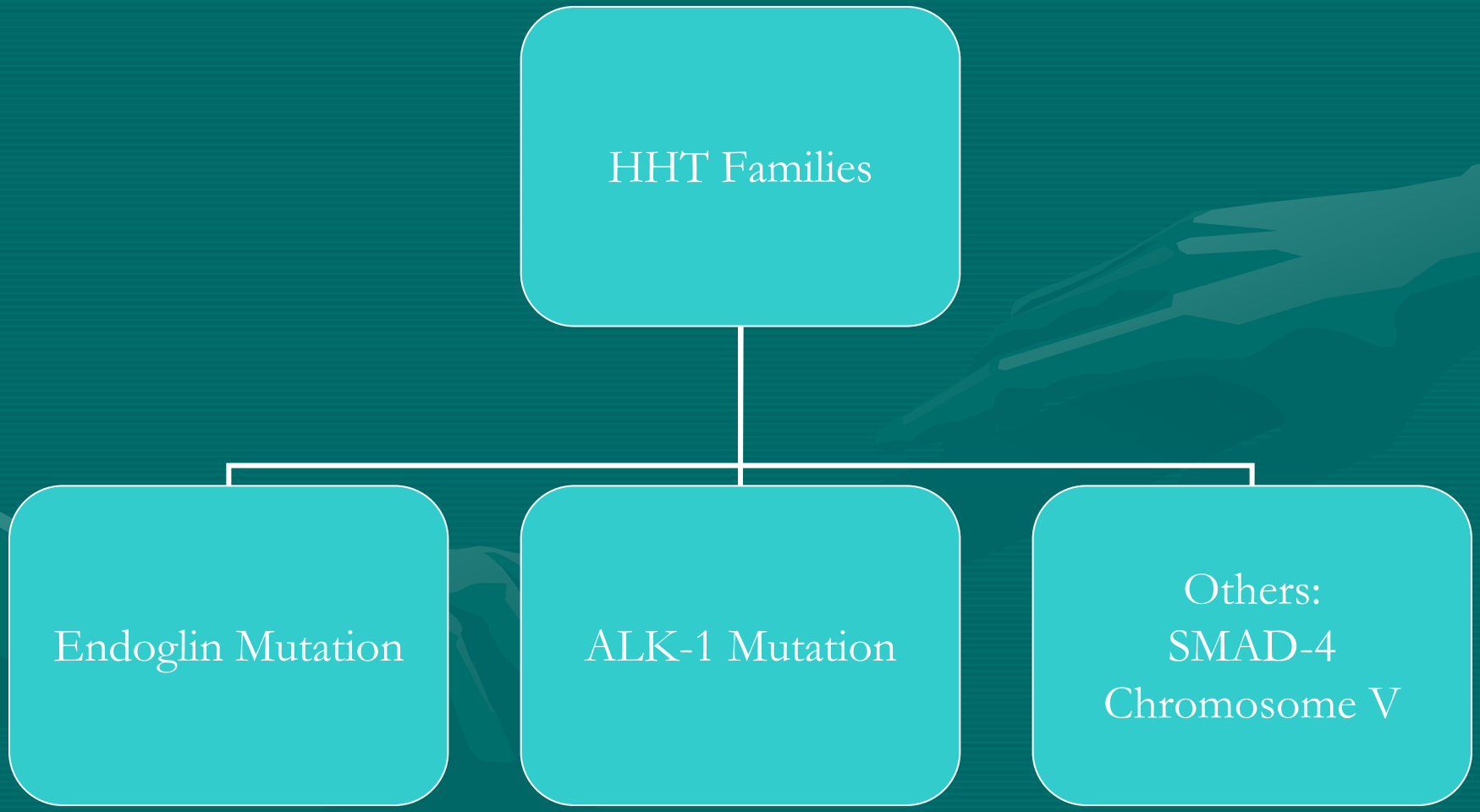
HHT related Mortality

- Denmark, population screening
- 1/6000 have HHT
- Mortality 2x greater in HHT, for <60yrs
  - Attributable to the disease

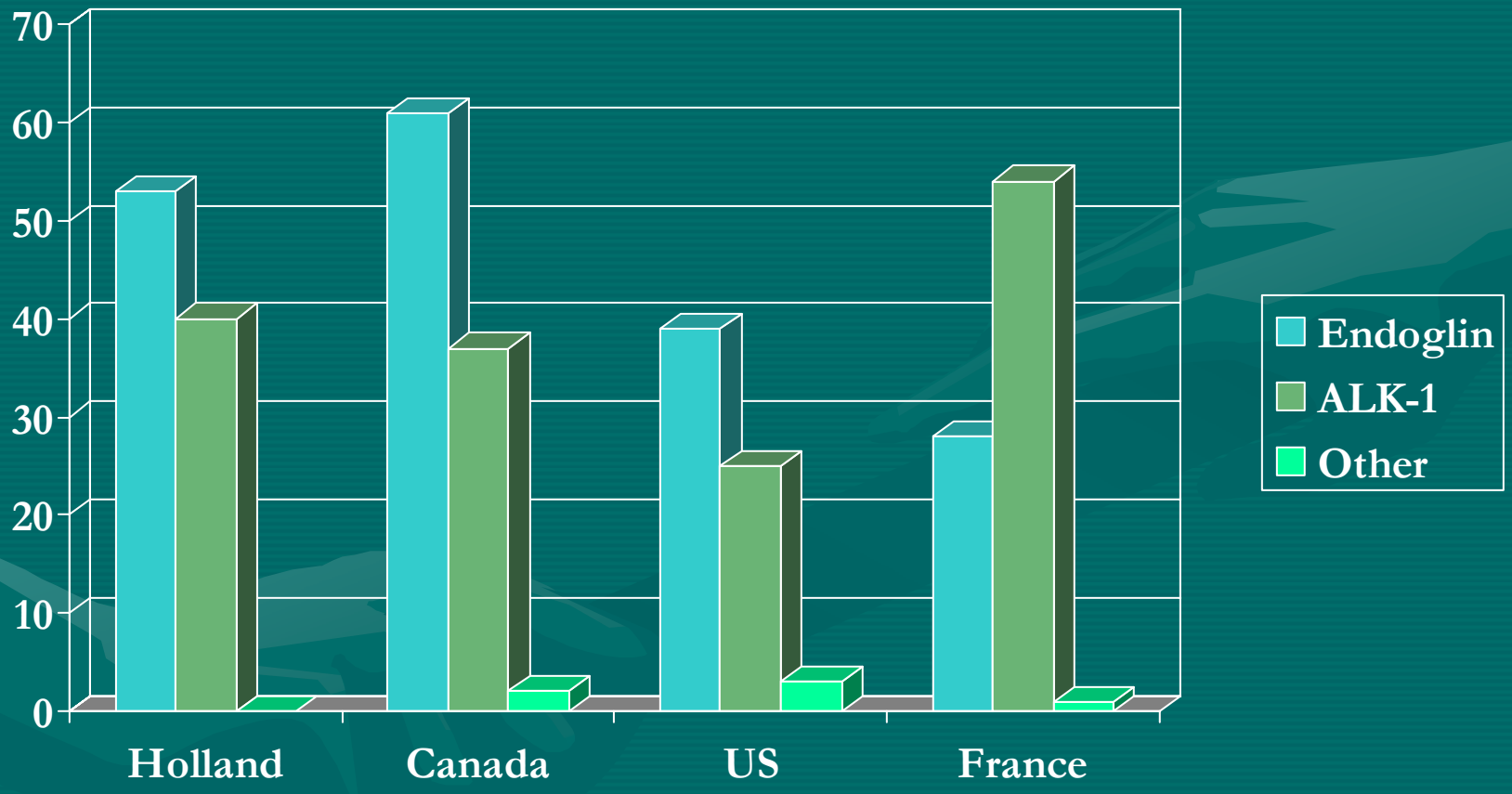
Fatale komplikationer til HHT er rapporteret i flere studier - således graviditetsrelateret pulmonal blødning (12, 13) og hjerneblødning på baggrund af bristet CAVM (3). Endvidere er der kliniske holdepunkter for øget hyppighed af gastrointestinal blødning med dødelig udgang (8, 9). Man har således antaget, at der er en øget dødelig blandt HHT-patienter (15). Det er imidlertid ikke tidligere verificeret.
Vi fandt, at HHT er associeret med en øget mortalitet. Dette var mest udtalt blandt de patienter, der var yngre end 60 år på

Kjeldsen A et al. Ugeskr Laeger 2000

Genetics of HHT



Genetics Internationally



Genotype-Phenotype Correlations

Manifest	Endoglin N=380	ALK-1 N=128	Unclass N=76	P-value
CAVM	15%	1%	10%	<0.001
PAVM	49%	5%	45%	<0.001
LVM	8%	41%	21%	<0.001*
GI bleed	72%	65%	69%	NS

Letteboer et al JMG 2005

Genotype-Phenotype Correlations

Organ	Endoglin N=69	ALK-1 N=207	P-value
Epistaxis			P<0.05
CAVM			NS
PAVM	70%	18%	P<0.05
LVM	43%	60%	NS
GI bleed			NS

Epistaxis earlier in HHT1 (12 vs 19yrs)

Lesca G et al Abstract Lyon 2005

Observations to Date

- Phenotypic heterogeneity within families
  - Of organ involvement
  - Severity of complications
- Phenotypic heterogeneity amongst families
  - Of frequency/type of organ involvement
  - Of complications

Phenotypic Heterogeneity

- She may only have epistaxis
- Her 2 children are asymptomatic
- Affected sister with PAVMs
- Unaffected sister
- Mother has epistaxis, GI bleeding
- Maternal grandmother had epistaxis

Another HHT Family

- Three generations seen (25 patients)
- ALL affected have PAVMs
- 1 has CAVMs
- 1 has gastrointestinal bleeding
- None have symptomatic LVMs

JP-HHT Syndrome

- 7 families with JP and HHT
- All found to have SMAD4 mutation
- 14 patients
- Epistaxis: 9/14 (64%)
- Telangiectasia: 9/14 (64%)
- CAVMs: 3/14 (21%) suspected
- PAVMs: 7/14 (50%)
- LVMs: 4/14 (29%)

Gallione C et al. Lancet 2004

SMAD4 in HHT Patients

- Unresolved families (N=30)
- HHT; no history JP
- 3 patients:
  - All had epistaxis and telangiectasia
  - PAVMs in 2
  - LVMs in 1
  - GI bleeding in 1
  - 2 have colon polyps, 1 with cancer
- No history of HHT in parents

Gallione C et al. JMG 2006

What makes HHT worse?

- Age
- Sex
- Hormonal changes
- Environment:
  - Cellular: hypoxia? Inflammation?
  - Indoor/personal: temperature, humidity, smoking, allergies
  - Outdoor: sun, pollution, temperature

HHT and Age

- Mostly cross-sectional data, rather than prospective observations on aging
- Expression versus progression
- Increased telangiectasia with age
- Changes in malformations structure?
- Potential explanations:
  - Damage to HHT vessels
  - More AVMs/telang form as repair vessels re cumulative injuries with age
  - Vessels become more fragile with aging?

Clinical Observations

Disease gets worse with age

- Increased number and size of mucocutaneous telangiectasia
- Vessels more fragile?
- Increased bleeding (nose, GI)
- Increased complications from shunt
  - Increased stroke from PAVMs…increased thrombosis?
  - Increased CHF from LVMs…reduced ability of heart to maintain high output?

Age-Related Expression

Manifestation	Prevalence	Age at 50% prevalence
Epistaxis	96%	20 yrs
Telangiectasia	74%	30 yrs
Visceral	25%	60 yrs
CAVMs	NSD	NSD
PAVMs	5%	38 yrs
GI bleed	15%	58 yrs
LVMs	8%	60 yrs

Plauchu H et al. AJMG 1989

Age and Epistaxis

- Mean age onset: 12 yrs
- 90% developed before age 21
- Symptoms progressive with age
- No difference between males and females

Severity	Mean age
Mild	22 yrs
Moderate	39 yrs
Severe	41 yrs*

Sami AAssar O. et al Laryngoscope 1991

CAVMs and Age

75 CNS VMs in 50 HHT patients

- Spinal AV fistulas: 6 mean age 2.2 yrs
- CAV Fistulas: 34 mean age 3.0 yrs
- CAVM (nidus): 16 mean age 23.1yrs
- Micro CAVMs: 18 mean age 31.8 yrs

Age related penetrance? Or age related complications?

Timing of injury determines morphology?

Krings T et al Neuroradiology 2005

GI Telangiectasia and Age

- 20 consecutive adults with HHT
  - EGD
  - Capsule endoscopy
- 75% had gastric telangiectasia
- 56% had small bowel telang (all had gastric)
- Patients with small bowel telangiectasia were older:
  - 63 yrs vs 45 yrs (p=0.02)
- Cumulative injury? Small bowel becomes more susceptible with age?

Ingrosso M et al. Endoscopy 2004

Sex and Clinical Presentation

- PAVMs increased in women HHT
  - 41% vs 55% p=.05

Letteboer et al JMG 2005

- Symptomatic LVMs
  - HHT1: women 11% vs men 2% NS
  - HHT2: women 55% vs men 17% NS
- Pregnancy: increased hemorrhage from PAVMs

Shovlin QJM 1995

- Menopause: increased epistaxis
- Hormonal effect different on mucosal versus visceral?

Environmental Effects? Distribution of Telangiectasia

- Sun exposed skin surfaces
- Mouth, nose, airways: exposed to environment, irritants, oxidants, infections, temp changes
- GI tract: exposed to food related toxins, acidity, trauma
- No human studies of any of these factors in HHT

Do AVMs grow?

- PAVMs in Adults:
  - Anecdotally from HHT MDs, case reports
  - Pollak JVIR 2006: 3-7 yrs f/u: 10% grow
  - RI White unpublished data
- PAVMs: echos with small shunt…probably have small PAVM…our experience is none new developing yet (7yrs)
- Liver? Uncertain natural history
- Not clearly for CAVMs

Pulmonary HTN

- Rare clinical problem in HHT
- Associated with ALK-1>Endoglin
- Outcomes? Are progression and prognosis similar to idiopathic PAH?

Human mechanistic research

- To date studying adults with established disease: are we studying early enough?
- TGF-beta
- VEGF
- Nitric Oxide

TGF-beta

- Humans (N=197) Serum TGF-beta:
  - Reduced in HHT1 patients
  - Normal in HHT2 patients
  - Inverse correlation with age for TGF-beta and Endoglin
- HUVEC
  - Reduced TGF-beta expression (mRNA)
  - Reduced Endoglin expression (mRNA)
  - Reduced secretion of TGF-beta

Letarte M et al. Cardiovasc Res 2005

VEGF

- 32 HHT patients
- 37 healthy controls
- Serum VEGF
- HHT: 196.3 +/- 103.2 pg/ml
- Controls: 152.0 +/- 84.1 pg/ml

P<0.03

Persistent activation phase of angiogenesis?

Cirulli A et al. Acta Heamatol 2003

Exhaled NO in HHT patients

Fraction	HHT	Healthy Controls	P-value
Airway NO	N=10 NOe=20.0ppb	N=6 NOe=32.9ppb	0.001
Alveolar NO	N=47 NOe=12.2ppb (SD=3.6)	N=46 NOe=10.8ppb (SD=3.1)	0.03

Suggests increased pulmonary capillary production of NO

Medical Therapies

Therapy	Target	Effective	Safety	Mechanism
E+P	GI bleed	+	+/-	?
E+P	Epistaxis	+/-	+/-	Metaplasia
Tran. Acid	Epistaxis/ GI	+/-	+/-	Antifibrinolytic
Danazol	GI bleed	+/-	+	
Sirolismus	Telang	+	+/-	VEGF inhibn
Thalidomide	GI bleed		+/-	?
Interferon	Telangiect	+	+/-	Anti-angiogenesis

Summary

- HHT characterized by vascular malformations
- Heterogeneity is the rule
- Increasing severity with age, female sex, environmental exposure?
- Most observations measures correlate with mouse model findings, some do not
- Need more mechanistic research in the human patient with HHT