소뇌실조증; 진단적 접근 및 감별진단

조 진 환
성균관대학교 의과대학 신경과학교실

Cerebellar ataxia: laboratory approach & differential diagnosis

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Contents

Unique Origin Unique Future

- Diagnostic flow of Cerebellar Ataxia
- Autosomal Dominant Cerebellar Ataxia
- Autosomal Recessive Cerebellar Ataxia
- Unusual Cases of Ataxia

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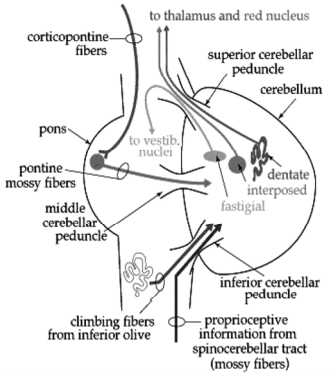
Symptoms of cerebellar dysfunction

- Ataxia
- Dysmetria
- Dyssynergia
- Dysrhythmia
- Dysdiadochokinesia
- Tremor
- Dysarthria
- Abnormal EOM
- Hypotonia
- Impaired motor learning



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When we meet cerebellar ataxia?

- What is the symptoms of cerebellar ataxia?
- How can we approach?
- How can we differentiate the ataxic disorders?
- Accuracy of final diagnosis?
- What is the issue in the management of ataxia?

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Diagnostic work up for Cerebellar ataxia

Taking history

Toxic exposure, Drug history, Family history, Alcohol, anoxic

Neurological Examination

⇒ Thinking : Differential Diagnosis

Blood test

CBC, glucose, electrolyte, ammonia, TFT, PTH, tumor markers, Vit B1/B12/E, folate, alpha-fetoprotein, copper, Zn, amino acid, lipid electrophoresis, serum Ig, lactate/pyruvate, antibodies for TG, microsomal, GAD, Yo, Hu, Ri.....

CSF study

NCS/EMG, muscle biopsy

Brain MRI/PET imaging

Genetic test

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Ataxia

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- **Sporadic ataxia**
  - **MSA**
  - **SAOA(ILOCA)**
  - Stroke
  - Tumor
  - toxic/metabolic
  - Paraneoplastic
  - Autoimmune
  - Infectious/post-infectious
  - Demyelinating
  - Other
- **Genetic (AD) Ataxia**
  - SCA/DRPLA
  - EA
- **Genetic (AR) Ataxia**
  - Friedreich Ataxia
  - Ataxia with isolated VitE defi
  - Abetalipoproteinemia
  - Ataxia telangiectasia
  - AOA
  - Mitochondrial recessive ataxia
  - Others

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Distribution of cerebellar ataxias in SMC Adult MD Clinic (2010-2012)

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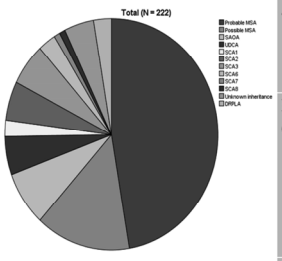
Table. Distribution of cerebellar ataxias



		n	%
Sporadic - Degenerative	Probable MSA-C	105	47.3
	Possible MSA-C	32	14.4
	SAOA	17	7.7
	UDCA	12	5.4
	Total	166	74.8
Familial or Genetic	SCA1	5	2.3
	SCA2	12	5.4
	SCA3	13	5.9
	SCA6	6	2.7
	SCA7	2	0.9
	SCA8	2	0.9
	DRPLA	6	2.7
	Unknown inheritance	10	4.5
	Total	56	25.2
Total		222	100

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Acute ataxia or subacute ataxia in clinic

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Alcohol consumption
Vitamine B1 deficiency
Drugs (CBZ, DPH, PB, lithium, FU, Metronidazole, amiodarone..)
Toxic agents (mercury, thallium, lead, toluene, pesticides, solvents...)
Stroke
Multiple sclerosis
Basilar Meningitis
Cerebellitis/Abscess
Paraneoplastic Syndrome
CJ disease

- **Sporadic ataxia**
  - MSA
  - SAOA(ILOCA)
  - **Stroke**
  - **Tumor**
  - **toxic/metabolic**
  - **Paraneoplastic**
  - **Autoimmune**
  - **Infectious/post-infectious**
  - **Demyelinating**
  - **Other**

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Sporadic degenerative ataxia

Terminology
- need consensus
- be careful to use term "MSA" in clinic

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Terminology in Ataxia

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Ataxia ≠ Cerebellar ataxia
Sensory Ataxia, Frontal dis-equilibirum

Cerebellar ataxia ≠ Cerebellar atrophy
ILOCA, SAOA ≠ CCA, OPCA

Cerebellar atrophy ≠ Olivopontocerebellar atrophy
CCA ≠ OPCA

ILOCA ≠ Sporadic OPCA
Not all idiopathic late-onset cerebellar ataxia(ILOCA) is OPCA
ILOCA : CCA + OPCA + normal cerebellum

Sporadic OPCA Progress to MSA (-)
Not all sporadic OPCA is MSA-C
ILOCA & sporadic OPCA : 25% evolve to MSA within 5 yrs

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Sporadic degenerative ataxia

What is MSA?

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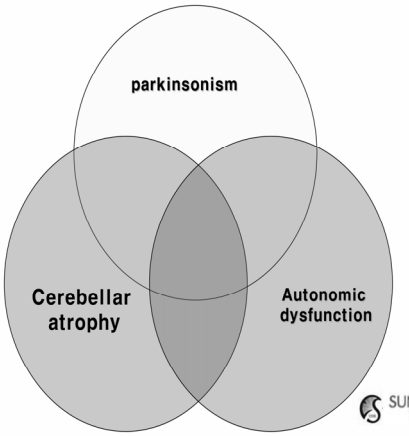
다계통위축증(Multiple system atrophy, MSA)



Diagnostic criteria for MSA (Gilman, 2008)

Striatonigral type (predominantly **parkinsonism**)		Olivopontocerebellar type (predominantly **cerebellar**)
	Sporadic progressive adult onset(>30Y)	
	Possible	
Parkinsonism		**Cerebellar** syndrome
	One feature of Autonomic dysfunction* At least one of the additional features of MSA**	
	Probable	
Autonomic failure **Poorly L-dopa responsive**		**Autonomic** failure **(urianry incontinence, Orthostatic Hypotension >30/15mmHg)**
Parkinsonism		**A cerebellar syndrome**
Postmortem confirmed	*Definite*	Postmortem confirmed

*: urgency, frequency, incomplete emptying, erectile dysfunction, standing BP↓
**: Babinski sign with hyperreflexia, stridor, rapid progressive Pism, postural instability, dysphagia, MRI finding, FDG-PET finding, presynaptic DA deficit

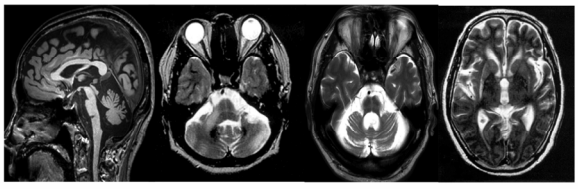
Pathology of MSA

- Selective neuronal loss & axonal degeneration : nigrostriatal system & pontocerebellar systems
- Intermediolateral columns and Onuf's nucleus
- Glial cytoplasmic inclusions(GCIs) within oligodendrocytes
- Glial nuclear inclusions, Neuronal cytoplasmic inclusions, neuronal nuclear inclusions

Imaging Studies in MSA

Putaminal Hyperintensity/Hypointensity
Hyperintense putaminal rim
Cerebellar Atrophy
Hyperinsensity in MCP (MCP sign)
Hot Cross burn Sign (80% of MSA-C; J neurol 2002)

Not always present in early stage
Need F/U



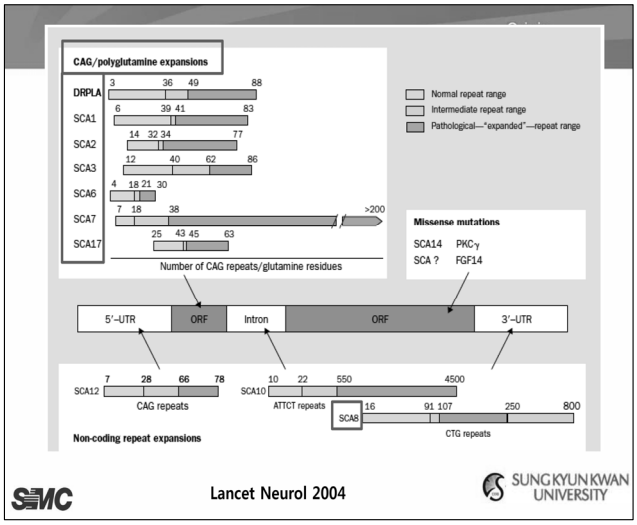
DAT scan, FDG PET : MSA-P .. MSA-C
MIBG scan : helpful to differentiate from PD

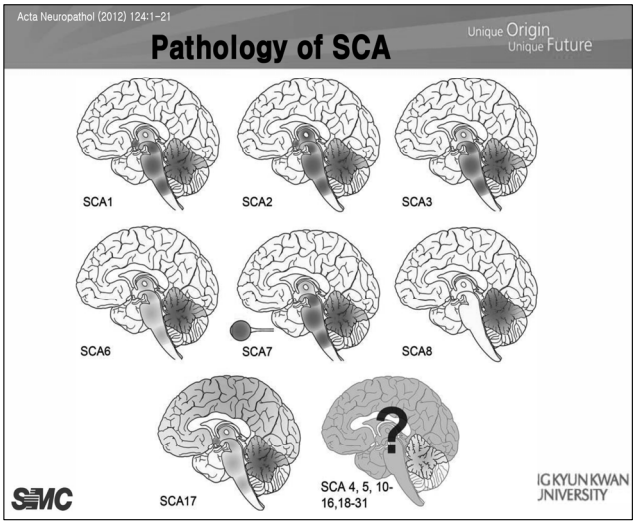
Cerebellar Ataxia

Autosomal Dominant :
SCA & DRPLA

Classification of Spinocerebellar ataxia

- **Classification by Harding (1993)**
  - **ADCA type I** : SCA1-SCA4, SCA8, SCA10, SCA12-SCA23, SCA25, SCA27, SCA28
    - accompanied by optic atrophy, ophthalmoplegia, extrapyramidal signs, neuropathy, and cognitive impairment
  - **ADCA type II** : SCA 7
    - characterized by retinal degeneration
  - **ADCA type III** : SCA5, SCA6, SCA11, SCA26, SCA29, SCA30, SCA31
    - pure cerebellar ataxia , often with a later age at onset





Polyglutamine expansion SCAs

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- nearly 50 % of autosomal-dominant ataxias
- Characteristics
  - : **genetic anticipation**
  - : **Genetic impriniting** - more pronounced from the paternal side
  - : **Somatic mosaicism**
- most striking in DRPLA and occurs only very rarely in SCA6.
- The expansion size of the **unaffected (trans) allele** can influence disease onset, as has been shown in SCA1 and SCA3.

SCA : genetic frequency

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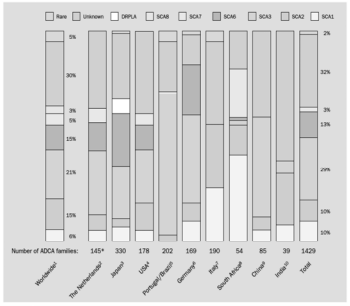
- **Epidemiological studies**
  - The prevalence of ADCAs - 3 in 100,000
  - SCA1, SCA2, SCA3, SCA6, SCA7, and SCA8 ≈ 50%
  - Commonest subtype worldwide; SCA 3 (SCA 2 in Korea)
  - Founder effect : great differences in different geographic regions



- **SCA 3**
  - high in…
    - Brazil (69%)
    - Portugal (58%)
    - China (49%)
    - Japan (26–63%)
    - Netherlands (28%)
    - Germany (42%)
  - lower in…
    - France (20%)
    - Canada (24%)
    - USA (21%)
  - rare in…
    - India (3%)
    - Norway (4%)
    - Italy (1%)

Lancet Neurol 2004

SCAs in Korea

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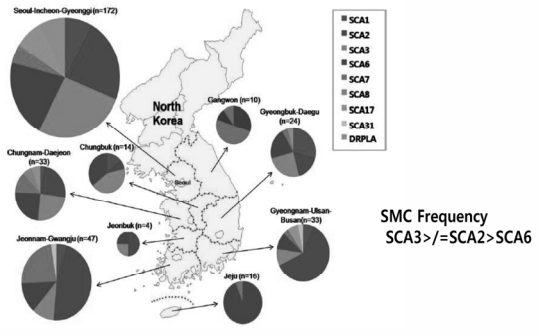

SMC Frequency
SCA3>/=SCA2>SCA6

<Korea>

Kim et al. PRD 2011

AD Ataxia : Genetic W/U

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Progressive cerebellar ataxia
+ dominant family history

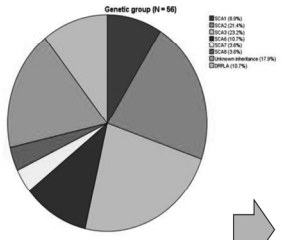
SCA Panel (1,2,3,6,7,8,17, DRPLA)

SCA_X $SCA_{unknown}$

Problems:

- **Family history can be negative!**
- **Ataxia can be minor!**
- **Which SCAs to test for?**

Genetic group of SCA in SMC



1. SCA distribution
: SCA3>/=SCA2>SCA6

2. Fhx (-)

- ✓ **11 (23.9%) subjects denied to have family history**
- ✓ **5 (10.9%) showed autosomal recessive inheritance pattern.**

DDx: SAOA(ILOCA) & MSA-C?

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Differntial Point 1. Clinical Phenotype

SCA 1

Onstet: 4th decade (6-60yrs)
Clinical feature: Gait ataxia → ophthalmoparesis, DTR loss
→ Severe dysphagia

SCA 2

Onstet: 4th decade (infancy to seventh decade)
Clinical feature: Gait/limb ataxia
Differential point : **Early Hyporeflexia & Slow saccades**

SCA 3

Young adult onset: rapidly progressive ataxia with pyramidal & EPS
Adult onset: moderate progressive ataxia, **EPS, Exo-ophtalmos**
Late adult onset: Slower progression of ataxia, prominent Peripheral nerve sign and few EPS

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Differntial Point 1. Clinical Phenotype

SCA 6

Onstet: 45-50yrs (20-75yrs)
Clinical feature: unsteady Gait (axial & Lower limb)
Differential point : **Downbeat Nsytagmus, Perverted Head-shaking Nystagmus, Pure ataxia,** ophthalmoparesis, DTR loss
Phenotype share: EA, Familial Hemiplegic Migraine (CACNA1A)

SCA 7

Onstet: 30 yrs (infancy to seventh decade)
Clinical feature: Gait/limb ataxia
Differential point: **Retinal degeneration, Slow saccades, retained DTR**

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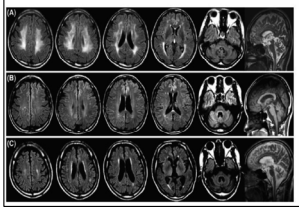
Differntial Point 1. Clinical Phenotype

SCA 17

Onstet: 19-48 yrs
Clinical feature: Gait ataxia and **dementia, EPS, Chorea**, Epilesy

DRPLA

Early onset (<20yrs): severe & rapid progression of myoclonus, epilepsy, cognitive decline
Later onset : ataxia, chorea, dementia, psychiatric problems



J Neurol
DOI 10.1007/s00415-011-6403-6

ORIGINAL COMMUNICATION

Is cerebral white matter involvement helpful in the diagnosis of dentatorubral-pallidoluysian atrophy?

Won Tae Yoon · Jinyoung Youn · Jin Whan Cho

SMC SUNG KYUN KWAN UNIVERSITY

Differntial Point 1. Clinical Phenotype

SCA 8

Onstet: 40 (infancy to 65yrs)
Clinical feature: Limb & gait ataxia, trunkal titubation, leg ataxia
Characteristics:
1) CTG repeat rather than CAG repeat & not coding RNA
2) Repeat length not correlate with severity
3) Allele expansion with maternal transmission (contraction with paternal transmission)
4) Variable expansion (no cut-off value)
5) Abnormal allele length in other neurologic disease & normal control (causative? Pathogenic role?)

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Return to Basic

Dissociation between
genotype & phenotype (++)
→ But ……..

조진환
신경학 2판 2012년

표 15-13 척수소뇌실조의 임상적 특징

발병나이	젊은 성인: SCA 1, 2, 3 장년: SCA 6 소아기발병: SCA 2, 7, DRPLA
현저한 대뇌림악화	SCA 7, DRPLA
상위운동신경세포징후	SCA 1, 3, > 7, 12
느린신속보기(slow saccade)	초기에 뚜렷: SCA 2, 7 말기: SCA 1, 3
감각말초신경병	SCA 1, 2, 3, 7
심부건반사 소실	SCA 2, 3(말기)
시력장애	SCA 7
치매	뚜렷: SCA 17, DRPLA 초기: SCA 2, 7
파킨슨증	SCA 2, 3, 17
근긴장이상	SCA 2, 3, 17
무도병	SCA 17, DRPLA
근간대경련	SCA 2, DRPLA
떨림	SCA 12
뇌전증	SCA 10, DRPLA

Differntial Point 2. Onset age & Progression

Table 2. Demographics of patients

	Genetic CA (n=56)	Sporadic CA (n=166)	*P*
Age(yr)*	51.2	57.8	<.05
F(%)	23(41.1%)	61(36.7%)	0.633
Onset age(yr)*	40.9	52.9	<.05
Disease duration(yr)*	10.34	4.9	<.05
Time from onset to diagnosis(yr)*	4.6	2.0	<.05
MMSE	26.8	26.2	0.274
ICARS at last assessment	38.8	33.2	0.095
Posture and gait disturbances	16.7	14.0	0.708
Kinetic functions	16.6	14.8	0.270
Speech disorders	2.9	2.7	0.482
Oculomotor Disorders*	2.5	1.6	<.05

SCA Onset : usually 30-40 yrs
Except SCA 6

Preparing data

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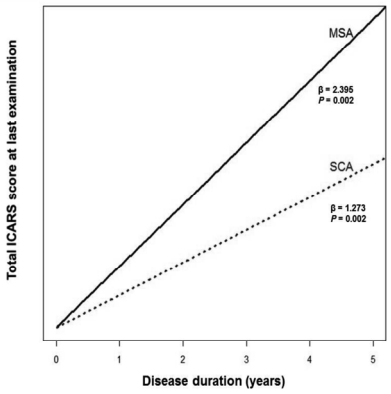
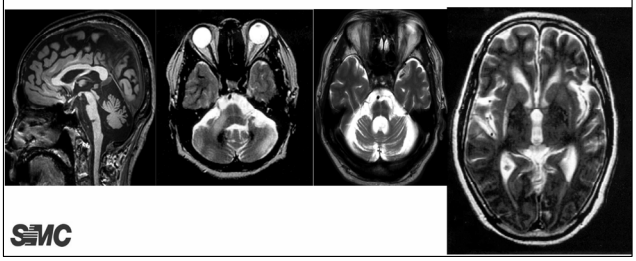
Progression pattern of ataxia: hospital based study



Preparing data

Differntial Point 3. Imaging Studies

Cerebellar Atrophy
Putaminal Hyperintensity/Hypointensity
Hyperintense putaminal rim
Hyperinsensity in MCP (MCP sign)
Hot Cross burn Sign



Differntial Point 3. Imaging Studies

Cerebellar Atrophy
Putaminal Hyperintensity/Hypointensity
Hyperintense putaminal rim
Hyperinsensity in the Middle cerebellar peducle (MCP sign)
Hot Cross burn Sign

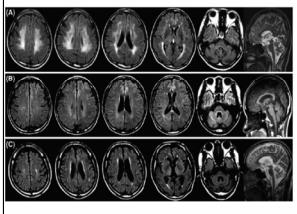
Table 1 The 'hot cross bun' sign and 'pontine midline hyperintensity' in the patients with genetically confirmed SCA and healthy controls

			T2-weighted MRI	
	No of patients (male/female)	Age (range)	Pontine midline hyperintensity (%)	Hot cross bun sign (%)
SCA	138 (69/69)	45.6 (13–86)	54 (39.1)	12 (8.7)
SCA1	3 (1/2)	37 (22–47)	2 (66.7)	0
SCA2	35 (17/18)	44.9 (13–74)	14 (40)	9 (25.7)
SCA3	76 (39/37)	42.3 (15–77)	38 (50)	1 (1.3)
SCA6	18 (8/10)	58.7 (39–83)	0	0
SCA7	1 (1/0)	59	0	1 (100)
SCA8	3 (2/1)	73.3 (62–86)	0	1 (33.3)
SCA17	2 (1/1)	51.5 (27–76)	0	0
Healthy controls	102 (55/47)	70 (55–91)	5 (4.9)	0

Lee et al. Eur Neurol 2009

Differntial Point 3. Imaging Studies

Significant White Matter change in DRPLA



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Differntial Point 4. Autonomic dysfunction

Spinocerebellar ataxia types 1, 2, 3, and 6

Disease severity and nonataxia symptoms

ABSTRACT

Objective: To identify factors that determine disease severity and clinical phenotype of the most common spinocerebellar ataxias (SCAs), we studied 526 patients with SCA1, SCA2, SCA3. or SCA6.

Methods: To measure the severity of ataxia we used the Scale for the Assessment and Rating of Ataxia (SARA). In addition, nonataxia symptoms were assessed with the Inventory of Non-Ataxia Symptoms (INAS). The INAS count denotes the number of nonataxia symptoms in each patient.

Results: An analysis of covariance with SARA score as dependent variable and repeat lengths of the expanded and normal allele, age at onset, and disease duration as independent variables led to multivariate models that explained 60.4% of the SARA score variance in SCA1, 45.4% in SCA2, 46.8% in SCA3, and 33.7% in SCA6. In SCA1, SCA2, and SCA3, SARA was mainly determined by repeat length of the expanded allele, age at onset, and disease duration. The only factors determining the SARA score in SCA6 were age at onset and disease duration. The INAS count was 5.0 ± 2.3 in SCA1, 4.6 ± 2.2 in SCA2, 5.2 ± 2.5 in SCA3, and 2.0 ± 1.7 in SCA6. In SCA1, SCA2, and SCA3, SARA score and disease duration were the strongest predictors of the INAS count. In SCA6, only age at onset and disease duration had an effect on the INAS count.

Conclusions: Our study suggests that spinocerebellar ataxia (SCA) 1, SCA2, and SCA3 share a number of common biologic properties, whereas SCA6 is distinct in that its phenotype is more determined by age than by disease-related factors. *Neurology*® 2008;71:982-989

Differntial Point 4. Autonomic dysfunction

Spinocerebellar ataxia types 1, 2, 3, and 6

Disease severity and nonataxia symptoms

Table 3 Frequency of nonataxia symptoms

	SCA1	SCA2	SCA3	SCA6	p
Hyperreflexia	67.5	13.2	40.1	21.9	<0.001
Areflexia	17.9	64.4	57.8	23.8	<0.001
Extensor plantar	50.5	31.0	41.9	2.0	<0.001
Spasticity	59.3	8.9	44.4	13.6	<0.001
Paresis	22.4	14.4	24.8	5.7	<0.001
Muscle atrophy	29.1	22.5	39.0	10.7	<0.001
Fasciculations	39.1	38.3	37.0	2.8	<0.001
Myoclonus	4.3	13.7	4.4	0.0	<0.001
Rigidity	1.7	7.4	10.3	5.7	NS
Chorea/dyskinesia	6.8	6.8	10.1	1.9	NS
Dystonia	12.8	14.2	23.9	4.7	<0.001
Resting tremor	6.8	14.9	3.6	1.9	<0.001
Sensory symptoms	62.4	68.4	65.6	48.0	NS
Urinary dysfunction	35.0	40.4	45.6	31.1	NS
Cognitive impairment	21.5	25.9	19.3	10.5	NS
Brainstem oculomotor signs	74.1	87.0	67.9	25.2	<0.001

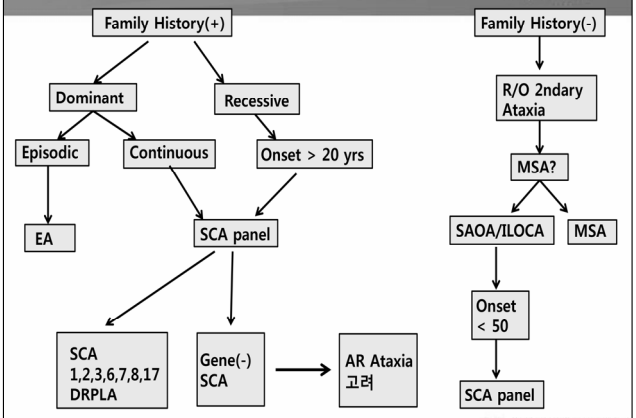
Autonomic dysfunction in MSA

- Autonomic dysfunction in normal elderly population

(J Urol 2008, J Clin Epidemiol 2000, Br J Nurs 2014)

- Urinary incontinence 20-40% in woman, 7-24% in Men
- Not considered the types of urinary incontinence
- Orthostatic Hypotension in normal elderly population (JAMA 1987)
- 6.4% (dec systolic BP greater than 20mmHg)
- Autonomic function test : not reliable to Dx of MSA
- Autonomic dysfunction not always present in early stage

Cerebellar ataxia: Autosomal Dominant



Cerebellar Ataxia

Autosomal Recessive Ataxia

AR Cerebellar ataxia in Korea

Table 2. Reports of cerebellar ataxia with an autosomal recessive inheritance pattern in Korea

Disease	Gene/product	Case	Clinical manifestations	Genetic confirm
FRDA	FXN/frataxin	Heo et al.[54]	Optic atrophy as the initial clinical manifestation	No
		Lee et al.[55]	Hearing difficulty, gait ataxia, scoliosis, proprioceptive loss	No
ATM	ATM/ATM protein	Jeong et al.[56]	Early onset ataxia, oculomotor apraxia, polyneuropathy, telangiectasia	Yes
		Huh et al.[57]	Early onset ataxia, oculomotor apraxia, telangiectasia	Yes
		Song et al.[58]	Early onset ataxia, frequent infections, telangiectasia	No
		Kang et al.[59]	Early onset ataxia, oculomotor apraxia, dysarthria, telangiectasia	No
CTX	CYP27A1/sterol-27 hydroxylase	Hwang et al.[60]	Ataxia, xanthomas, dementia, cranial nerve palsy, pyramidal signs, cataracts	No
		Suh et al.[61]	Xanthomas, cataract, osteopenia, mental retardation, ataxia, neuropathy	Yes
ARSACS	SACS/sacsin	Unpublished	Early onset ataxia, spasticity, distal amyotrophy with foot deformity	Yes
FXTAS	FMR1/FMRP protein	Ehm et al.[62]	Gait ataxia, parkinsonism, mood disorder, high signal in MCP	Yes

FRDA: Friedreich's ataxia, ATM: ataxia telangiectasia, CTX: cerebrotendinous xanthomatosis, ARSACS: autosomal recessive spastic ataxia of Charlevoix-Saguenay, FXTAS: Fragile X-associated tremor/ataxia syndrome.

Kim & Cho, JMD 2015

+ 2 cases of Niemann-Pick type C : presenting cerebellar ataxia

Autosomal Recessive Ataxia

Friedreich's ataxia (FA)
Ataxia with Vitamine E deficiency (AVED)
Abeta-lipoproteinemia
Ataxia telangiectaxia (AT)
Ataxia with oculomotor apraxia type 1, 2 (AOA)
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)
Cerebrotendionous xanthomatosis (CTX)
Autosomal recessive cerebellar ataxia type 1, 2 (ARCA)
Nieman-Pick type C disease (NPC)
Refsum's disease
Mitochondrial recessive ataxia syndrome (MIRAS)
Early onset cerebellar ataxia with retained reflexes
Sensory axonal neuropathy with dysarthria & ophthalmoplegia(SANDO)

Differntial Point 1. Hx & Ex

Unique Origin Unique Future

Age at onset
< 10 yrs : AT, AOA type 1, ARSACS, Abeta-lipoproteinemia
> 10 yrs : SANDO, ARCA 1

Progression
Slow: ARSACS, ARCA 1, ARCA 2
Rapid: AT, AOA 1, FA

Oculomotor impairment
: AT, AOA 1, AOA 2, FA, SANDO, NPC

Pyramidal signs
: CTX, ARSACS, FA, AVED

Movement disorders
: AT, AOA 1, AOA 2, NPC, AVED, SANDO

Mental Retardation (cognitive decline)
: AOA 1, ARSACS, ARCA 2, SANDO, NPC

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Differntial Point 2. Labs

Unique Origin Unique Future

Brain MRI
Normal : FA, AVED, Abeta-lipoproteinemia, Refsum's disease
Linear Hypointensities in the Pons : ARSACS

NCS/EMG
SM neuropathy: AOA 1,2, AT, CTX, ARSACS, Refsum's disease
Pure sensory Neuropathy: FA, AVED, Abeta-lipoproteinemia, SANDO
No Neuropathy : ARCA 1, ARCA 2, NPC

Biomarkers
Vitamine E: AVED, Abeta-lipoproteinemia
Alpha-fetoprotein: AT, AOA 2

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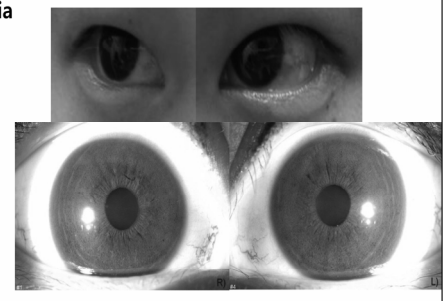
Differntial Point 3. Clinical findings

Unique Origin Unique Future

Ataxia-Telangiectasia



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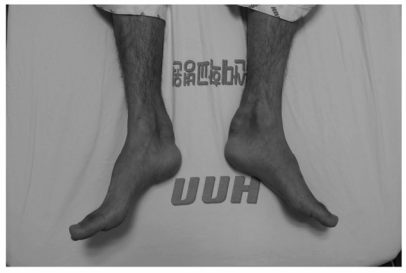
Differntial Point 3. Clinical findings

Unique Origin Unique Future

Cerebrotendionous xanthomatosis (CTX)



Courtesy of Pf Yang

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Differntial Point 3. Clinical findings

Unique Origin Unique Future

Nieman-Pick type C disease (NPC)

Vertical supranuclear gaze palsy

splenomegaly

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Approach to Recessive ataxia

Unique Origin Unique Future

Young age onset Ataxia (< 20 yrs)
AR or sporadic progressive ataxia
without Prominent Autonomic dysfunction

Fundoscopic examination
Blood smear
Vitamin E
Cholesterol
Alpha-fetoprotein
Immunological studies
Hormonal study (include TFT, DM)
Lactate/pyruvate
Brain Imaging (MRI...)
NCS & EMG

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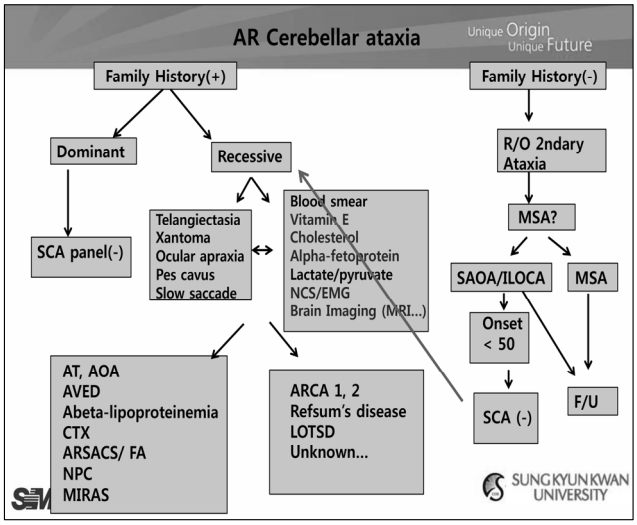
AR Cerebellar ataxia
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Family History(+)
Family History(-)
Dominant
Recessive
R/O 2ndary Ataxia
SCA panel(-)
Telangiectasia
Xantoma
Ocular apraxia
Pes cavus
Slow saccade
Blood smear
Vitamin E
Cholesterol
Alpha-fetoprotein
Lactate/pyruvate
NCS/EMG
Brain Imaging (MRI...)
MSA?
SAOA/ILOCA
MSA
Onset < 50
AT, AOA
AVED
Abeta-lipoproteinemia
CTX
ARSACS/ FA
NPC
MIRAS
ARCA 1, 2
Refsum's disease
LOTSD
Unknown...
SCA (-)
F/U
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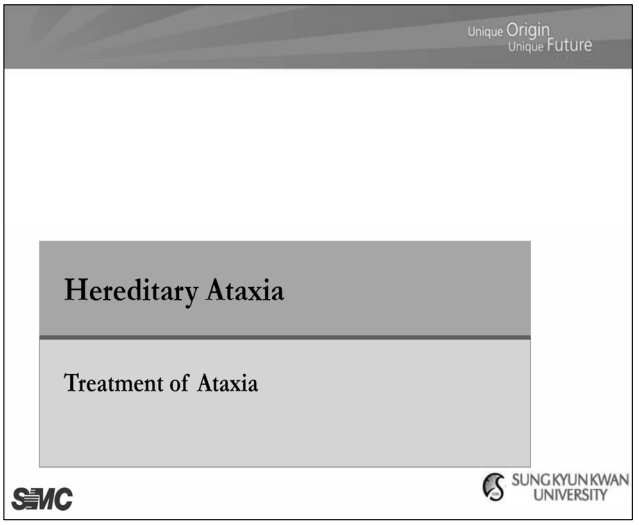
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Hereditary Ataxia
Treatment of Ataxia
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SMC protocol to treat Ataxia
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Exercise
Cerebrotonics (Football-Goal Keeper)
Emotional Encourage
IV Amantadine trial (JMD 2012)
Preliminary Study of Intravenous Amantadine Treatment for Ataxia Management in Patients with Probable Multiple System Atrophy with Predominant Cerebellar Ataxia
Journal of Movement Disorders 2012;5:1-4
Stem cell therapy
盡人事待天命
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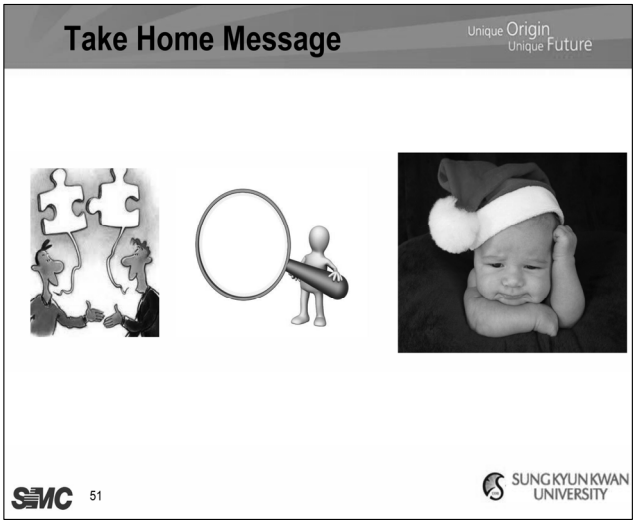
Take Home Message
Unique Origin Unique Future
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