DG Ataxia and HSP
November 5th, 2019

Cerebellar ataxia

a clinical approach

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European Reference Network for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

ean european academy of neurology

European Reference Network for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

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General information on the Webinars

30-35min presentation

15 min Q&A session

<u>Target audience</u>:
Neurologists, residents, paediatric neurologists, geneticists from RND members, RND affiliated partners, and non-RND HCPs across Europe

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Webinar outline

- Short introduction
- Diagnostic approach based on three scenario’s
- Therapeutic options
- Key points
- Voice of the patients
- Q & A

Learning objectives

- To have a clinical framework for the cerebellar ataxias
- To be able to make a differential diagnosis in an ataxia patient
- To know the first diagnostic (including genetic) steps
- To learn about the current treatment options for ataxia

Ataxia

Cerebellar
disturbance of oculomotor function and speech

Sensory
more apparent upon eye closure

Frontal
'higher level' gait disorder
other frontal signs

Vestibular
Veering to one side
Often acute onset, short-lasting, or episodic

Cerebellar ataxia – *clinical examination*

FOCUS	PERFORM	LOOK FOR
Eyes	Fixation Pursuit Saccades	Fixation instability / square-wave jerks Gaze-evoked nystagmus Jerky, interrupted pursuit Multistep saccades, overshoot saccades
Speech	Spontaneous speech, PATA repetition	Slurred, scanning speech
Arms	Finger-nose test Finger-chase test	Decomposition of movement (non-fluent) Dysmetria Action and/or intention tremor
Trunk	Sitting without support	Truncal sway
Legs	Heel-to-shin test	Action tremor and dysmetria (heel-to-knee) Decomposition of movement Sliding of the shin (heel-shin slide)
Stance	Tandem stance Normal stance	Unable to stand tandem Wide base of support Postural sway
Gait	Normal gait, including turns Tandem gait	Broad-based gait Deviation from straight line Variable stride length, step width and rhythm Unstable when turning Difficulty in walking tandem

SARA

Scale for the assessment and rating of ataxia

Development of a new clinical scale

T. Schmitz-Hübsch, MD; S. Tezenas du Montcel, MD, PhD; L. Baliko, MD; J. Berciano, MD; S. Boesch, MD; C. Depondt, MD; P. Giunti, MD; C. Globas, MD; J. Infante, MD; J.-S. Kang, MD; B. Kremer, MD; C. Mariotti, MD; B. Melegh, MD, PhD; M. Pandolfo, MD; M. Rakowicz, MD; P. Ribai, MD; R. Rola, MD; L. Schöls, MD; S. Szymanski, MD; B.P. van de Warrenburg, MD; A. Dürr, MD; and T. Klockgether, MD

Abstract—*Objective:* To develop a reliable and valid clinical scale measuring the severity of ataxia. *Methods:* The authors devised the Scale for the Assessment and Rating of Ataxia (SARA) and tested it in two trials of 167 and 119 patients with spinocerebellar ataxia. *Results:* The mean time to administer SARA in patients was 14.2 ± 7.5 minutes (range 5 to 40). Interrater reliability was high, with an intraclass coefficient (ICC) of 0.98. Test-retest reliability was high with an ICC of 0.90. Internal consistency was high as indicated by Cronbach's α of 0.94. Factorial analysis revealed that the rating results were determined by a single factor. SARA ratings showed a linear relation to global assessments using a visual analogue scale, suggesting linearity of the scale ($p < 0.0001$, $r^2 = 0.98$). SARA score increased with the disease stage ($p < 0.001$) and was closely correlated with the Barthel Index ($r = -0.80$, $p < 0.001$) and part IV (functional assessment) of the Unified Huntington's Disease Rating Scale (UHDRS-IV) ($r = -0.89$, $p < 0.0001$), whereas it had only a weak correlation with disease duration ($r = 0.34$, $p < 0.0002$) *Conclusions:* The Scale for the Assessment and Rating of Ataxia is a reliable and valid measure of ataxia, making it an appropriate primary outcome measure for clinical trials.

NEUROLOGY 2006;66:1717–1720

Focus on chronic, slowly progressive ataxias

Question 1

A male patient of 62 years is having gait and balance difficulties since three years. More recently, he has noticed speech problems. Clinical examination shows signs of cerebellar ataxia, with no other abnormalities. Brain imaging shows cerebellar atrophy.

In this patient, a screen for paraneoplastic antibodies should be initiated.

1. I agree
2. I do not agree

Etiological categories

Non-genetic cerebellar ataxia

a. acquired/symptomatic

b. degenerative

Genetic cerebellar ataxia

Etiological categories

Non-genetic cerebellar ataxia

a. acquired/symptomatic

b. degenerative

Genetic cerebellar ataxia

Use:

Age at onset

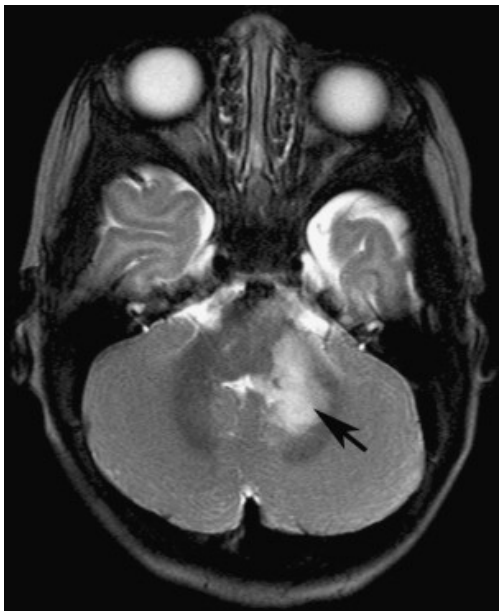
Acute vs. subacute vs. insidious onset

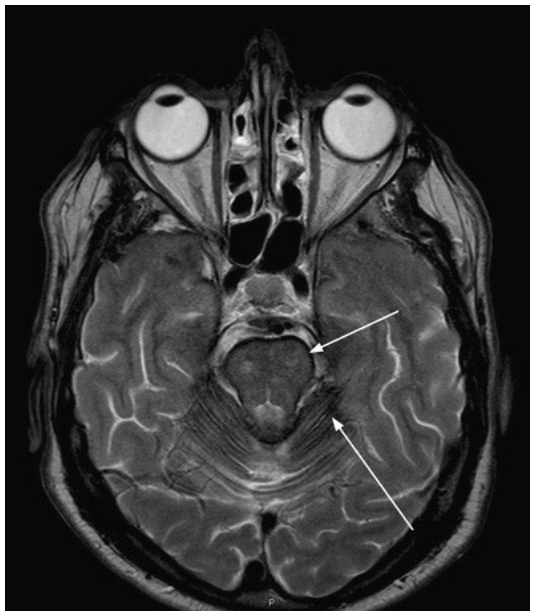
Speed of progression

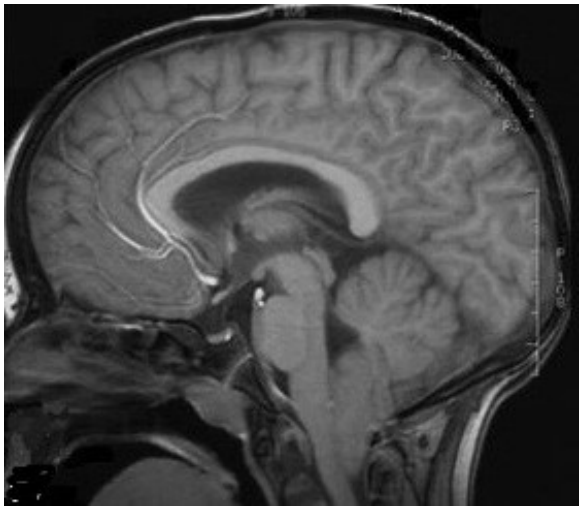
Family history

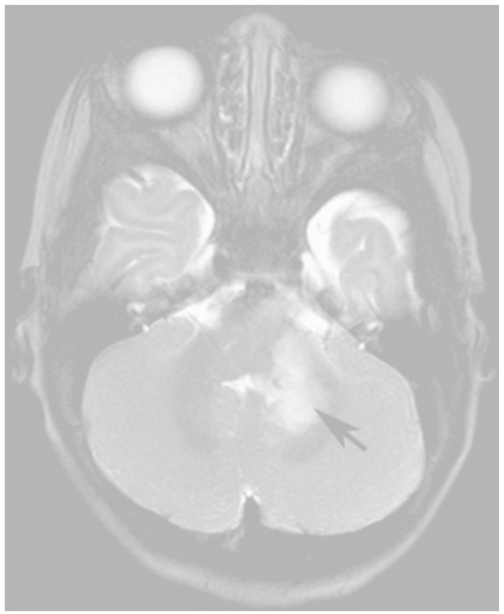
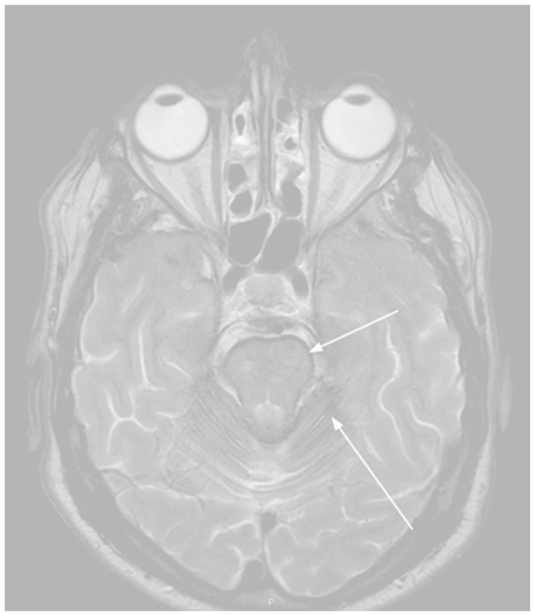
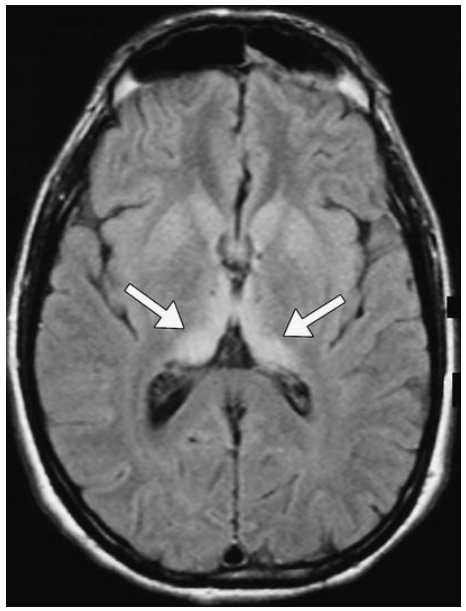
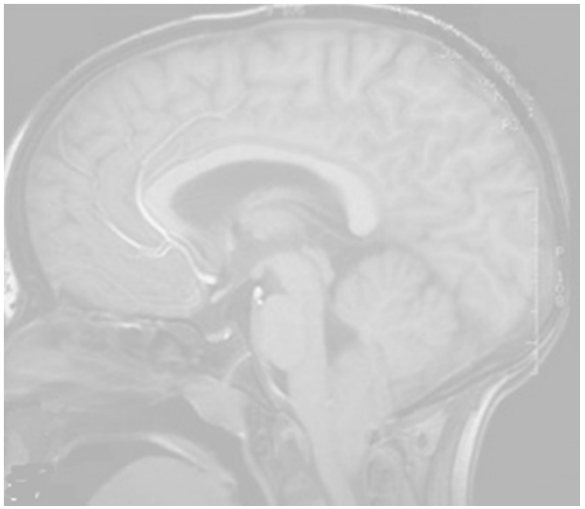
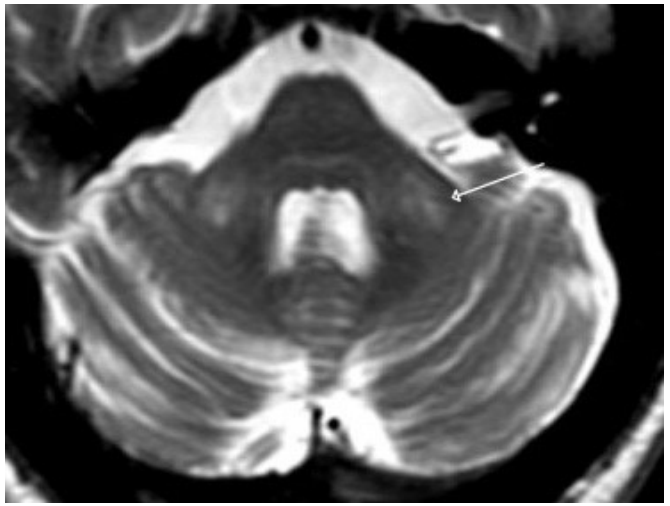
Context (malignancy, alcohol, drugs)

Other symptoms and signs





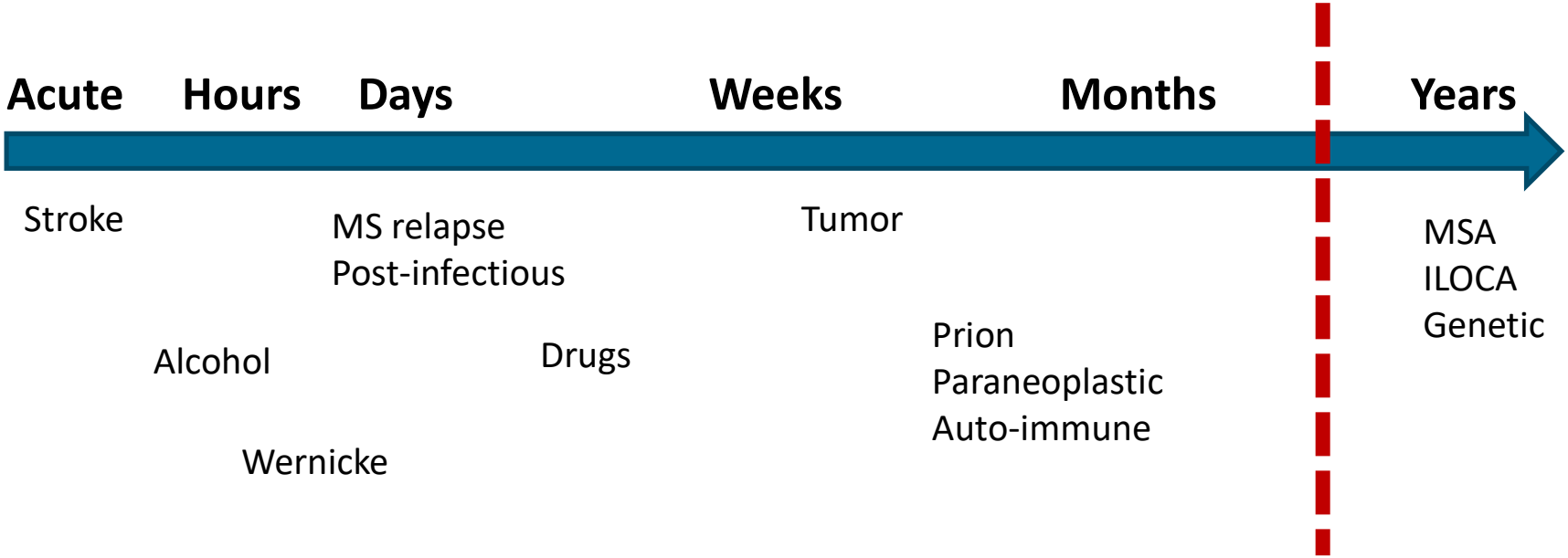


Subacute ataxia = acquired

- **Structural lesion**
- **Metabolic**
  - B1/B12 deficiency
  - hypoparathyroidism, hypomagnesiaemia
- **Immune-mediated / inflammatory**
  - post/para-infectious
  - paraneoplastic cerebellar degeneration
  - non-paraneoplastic Ab's: anti-GAD, anti-CASPR2, anti-DPPX, a.o.
  - CLIPPERS
  - SREAT
- **Drugs**
- **Prion disease**
- …..and others

Subacute ataxia = acquired



Focus on chronic, slowly progressive ataxias

Etiological categories

Non-genetic cerebellar ataxia

a. acquired/symptomatic

b. degenerative

Genetic cerebellar ataxia

3 scenario’s based on family history

1. Dominant
2. Recessive
3. Sporadic

3 scenario’s based on family history

1. **Dominant**
2. **Recessive**
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Etiological categories

Non-genetic cerebellar ataxia

a. acquired/symptomatic

b. degenerative

Genetic cerebellar ataxia

Question 2

The current number of genes associated with ataxia is around:

1. 50
2. 100
3. 150
4. 300

Genetic ataxia – general comments

Genetic classifications are messy

VIEWS & REVIEWS

Fixing the broken system of genetic locus symbols

Parkinson disease and dystonia as examples

Neurology® 2012;78:1016-1024

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Neurology® 2012;78:1016-1024

GENETICS SERIES: REVIEW

CME

Nomenclature of Genetic Movement Disorders: Recommendations of the International Parkinson and Movement Disorder Society Task Force

Connie Marras, MD, PhD,[1] Anthony Lang, MD,[1] Bart P. van de Warrenburg, MD, PhD,[2] Carolyn M. Sue, MBBS, PhD,[3] Sarah J. Tabrizi, MBChB, PhD,[4] Lars Bertram, MD,[5,6] Saadet Mercimek-Mahmutoglu, MD, PhD,[7] Darius Ebrahimi-Fakhari, MD,[8,9] Thomas T. Warner, BMBCh, PhD,[10] Alexandra Durr, MD, PhD,[11] Birgit Assmann, MD,[12] Katja Lohmann, PhD,[13] Vladimir Kostic, MD, PhD,[14] and Christine Klein, MD[13]*

Genetic ataxia – general comments

Genetic classifications are messy

Almost 150 genes

NGS diagnostics!

Precise phenotyping still required

Useful to recognize certain clinical syndromes, e.g. spastic ataxia

3 scenario’s based on family history

1. **Dominant**
2. Recessive
3. Sporadic

Autosomal dominant cerebellar ataxias

- ADCA or SCA
- Prevalence: 3 to 5 per 100,000
- Onset between 30 and 50 years (range 1 – 80)
- Progressive cerebellar syndrome
- Spectrum of additional, non-ataxia features
- SCA1 to SCA48

MUTATIONAL MECHANISM	LOCUS	*GENE*
Coding CAG repeat expansion		
SCA1	6p22-23	*SCA1*
SCA2	12q23-24.1	*SCA2*
SCA3	14q24-qter	*SCA3/MJD*
SCA6	19p13	*CACNA1A*
SCA7	3p12-21.1	*SCA7*
SCA17	6q27	*TBP*
Non-coding repeat expansion		
SCA12 (CAG)	5q31-33	*PPP2R2B*
SCA8 (CTG)	13q21	*SCA8*
SCA10 (ATTCT)	22q13-qter	*SCA10*
SCA36 (GGCCTG)	20p13	*NOP56*
Other mutations		
SCA5	11q13	*SPTBN2*
SCA11	15q14	*TTBk2*
SCA13	19q13	*KCNC3*
SCA14	19q13.4-qter	*PRKCG*
SCA15/16	3p26	*ITPR1*
SCA19	1p21-q21	*KCND3*
SCA21	1p36	*TMEM240*
SCA23	20p12.3-13	*PDNY*
SCA26	19p13.3	*eEF2*
SCA27	13q34	*FGF14*
SCA28	18p11.22-q11.2	*AFG3L2*
SCA31	16q22	*TK2/BEAN*
SCA34	6q14	*ELOVL4*
SCA35	20p13-12.2	*TGM6*
SCA38	6p12	*ELOVL5*
SCA40	14q32	*CCDC88C*
SCA41	4q27	*TRPC3*
SCA42	17q21	*CACNA1G*
SCA43	3q25	*MME*
SCA44	6q24	*GRM1*
SCA45	5q32	*FAT2*
SCA46	19q13	*PLD3*
SCA47	1p35	*PUM1*
SCA48	16p13	*STUB1*

MUTATIONAL MECHANISM	LOCUS	*GENE*
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SCA15/16	3p26	*ITPR1*
SCA19	1p21-q21	*KCND3*
SCA21	1p36	*TMEM240*
SCA23	20p12.3-13	*PDNY*
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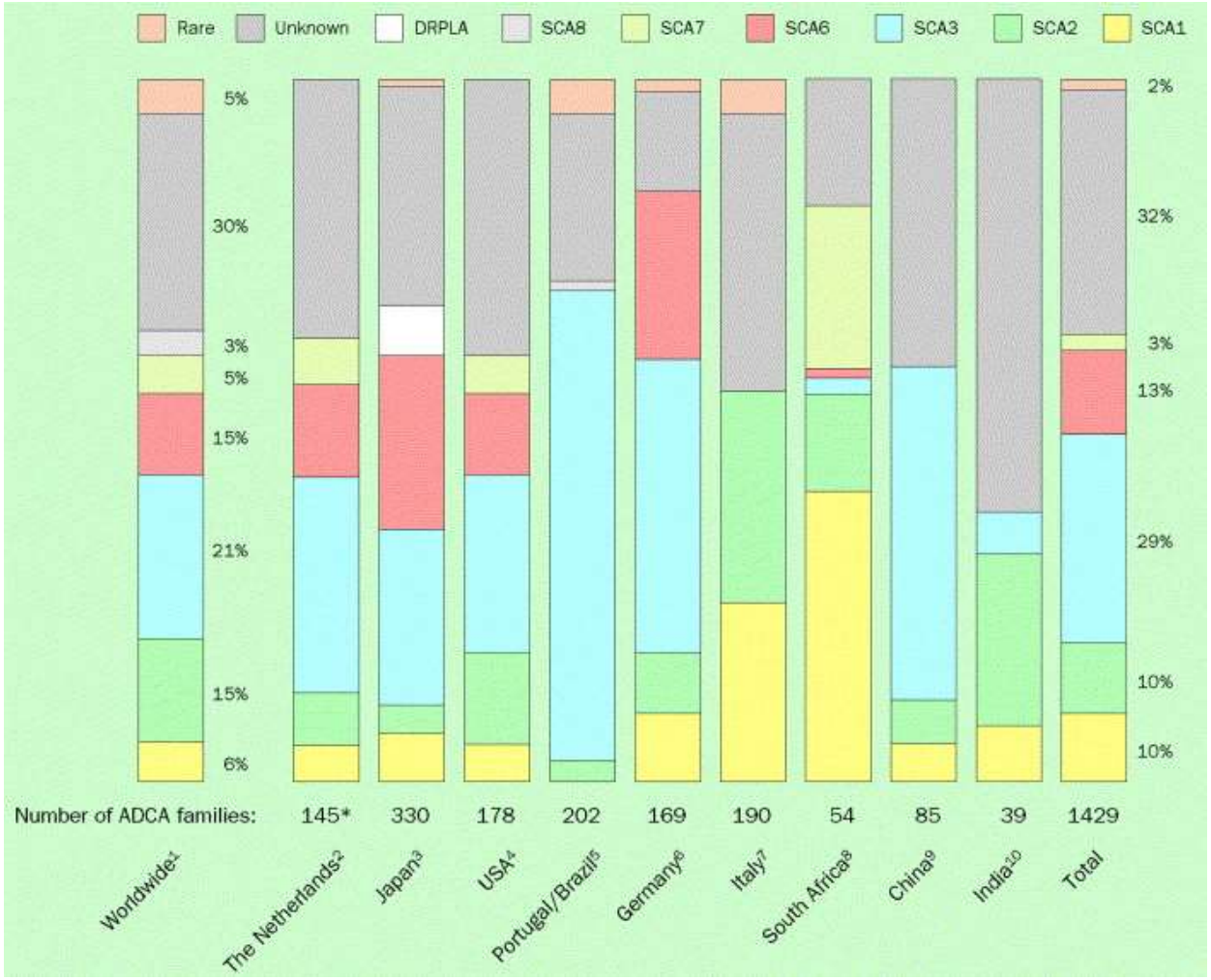
SCA34	6q14	*ELOVL4*
SCA35	20p13-12.2	*TGM6*
SCA38	6p12	*ELOVL5*
SCA40	14q32	*CCDC88C*
SCA41	4q27	*TRPC3*
SCA42	17q21	*CACNA1G*
SCA43	3q25	*MME*
SCA44	6q24	*GRM1*
SCA45	5q32	*FAT2*
SCA46	19q13	*PLD3*
SCA47	1p35	*PUM1*
SCA48	16p13	*STUB1*

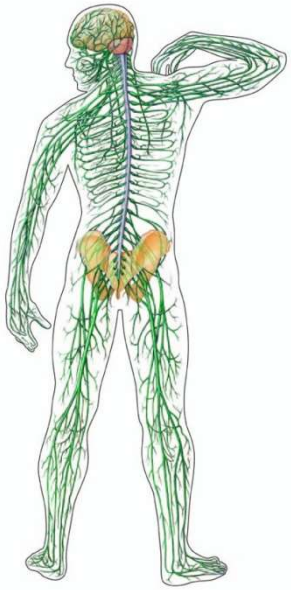

Rare
Unknown
DRPLA
SCA8
SCA7
SCA6
SCA3
SCA2
SCA1
5%
30%
3%
5%
15%
21%
15%
6%
2%
32%
3%
13%
29%
10%
10%
Number of ADCA families:
145*
330
178
202
169
190
54
85
39
1429
Worldwide[1]
The Netherlands[2]
Japan[3]
USA[4]
Portugal/Brazil[5]
Germany[6]
Italy[7]
South Africa[8]
China[9]
India[10]
Total

SCA's with CAG repeat expansions

- SCA1-2-3-6-7-17 (and DRPLA)
- The more common ones
- Not reliably detected by NGS platforms
- Check for these first
- CAG repeat length does not allow for individual predictions
- Exciting therapeutic developments (antisense oligonucleotides)

Non-cerebellar features

- Cognition: frontal executive, dementia
- Brainstem oculomotor function: slow saccades, ophthalmoparesis
- Pyramidal signs
- Deep sensory disturbances
- Peripheral neuropathy, motor neuron involvement
- ‘Extrapyramidal’ movement disorders
- Bladder symptoms
- Sleep disorders, restless legs
- ....



Verbeek DS & van de Warrenburg BP. Sem Neurol 2012.

	Locus	Gene	Mutation	Possible Distinguishing Features, Other Remarks
SCA1	6p23	ATXN1	CAG repeat	Pyramidal features, neuropathy, ophthalmoparesis
SCA2	12q24.1	ATXN2	CAG repeat	Slow saccades, parkinsonism, myoclonus, dementia
SCA3	14q21	ATXN3	CAG repeat	Known as Machado-Joseph disease, (extra)pyramidal features, neuropathy, motor neuron disease
SCA4	16q22.1	–	–	Marked sensory neuropathy
SCA5	11q13	SPTBN2	Missense, inframe deletions	Pure
SCA6	19p13	CACNA1A	CAG repeat	Relatively late-onset (mean 50 years)
SCA7	3p21.1-p12	ATXN7	CAG repeat	Visual loss due to retinal degeneration, dementia
SCA8	13q21	ATXN8OS	CTG repeat	Relatively pure
SCA9	–	–	–	Similar to SCA3
SCA10	22q13.31	ATXN10	ATTCT repeat	Seizures
SCA11	15q15.2	TTBK2	Frameshift deletion, small insertion	Pure
SCA12	5q32	PPP2R2B	CAG repeat	Head and hand tremor, parkinsonian features
SCA13	19q13.33	KCNC3	Missense	Childhood onset, mental retardation
SCA14	19q13.4	PRKCG	Missense, deletion, splice site	Myoclonus or dystonia
SCA15/16	3p26.1	ITPR1	Deletion, missense	Head and hand tremor
SCA17	6q27	TBP	CAG repeat	Chorea, dementia, parkinsonism
SCA18	7q22–32	–	–	Marked neuropathy
SCA19	1p21-q21	–	–	Myoclonus, frontal executive dysfunction
SCA20	11q12		260kb duplication	Palatal tremor, dysphonia, dentate calcification on CT
SCA21	7p21.3-p15.1	–	–	Parkinsonian features
SCA22	1p21-q21	–	–	Allelic to SCA19?
SCA23	20p13	PDYN	Missense	Pure
SCA24	1p36	–	–	Autosomal recessive (SCAR4)
SCA25	2p21-p13	–	–	Marked neuropathy
SCA26	19p13.3	–	–	Pure
SCA27	13q34	FGF14	Missense, 1 bp deletion	Onset with hand tremor, orofacial dyskinesia
SCA28	18p11	AFG3L2	Missense, 2 bp deletion/insertion	Ophthalmoparesis
SCA29	3p26	–	–	Congenital, nonprogressive ataxia
SCA30	4q34.3-q35.1	–	–	Pure
SCA31	16q21	TK2-BEAN1	TGGAA repeat	Hearing loss
SCA32	7q32–33	–	–	Azoospermia and cognitive impairment
SCA34	6q	–	–	Erythrokeratodermia. Not formally assigned
SCA35	20p13	TGM6	Missense	Pyramidal features, cervical dystonia
SCA36	20p13	NOP56	GGCCTG repeat	Motor neuron involvement

So, these non-cerebellar features

.... sometimes help us to predict the underlying genotype

But, in general

.... there is too much overlap, which prevents very selective testing

Diagnostic testing

1. Check for repeat expansions first

2. If available: do NGS (ataxia panel, exome sequencing)

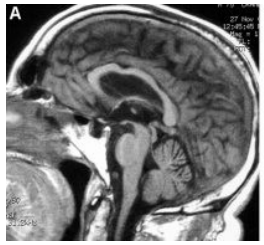
3 scenario’s based on family history

1. Dominant
2. **Recessive**
3. Sporadic

Autosomal recessive cerebellar ataxias

- ARCA or SCAR
- Affected sibs + healthy parents, and/or consanguinity
- Forget typical onset ages !
- Cerebellar, non-cerebellar, systemic features
- Phenotypic precision still has value

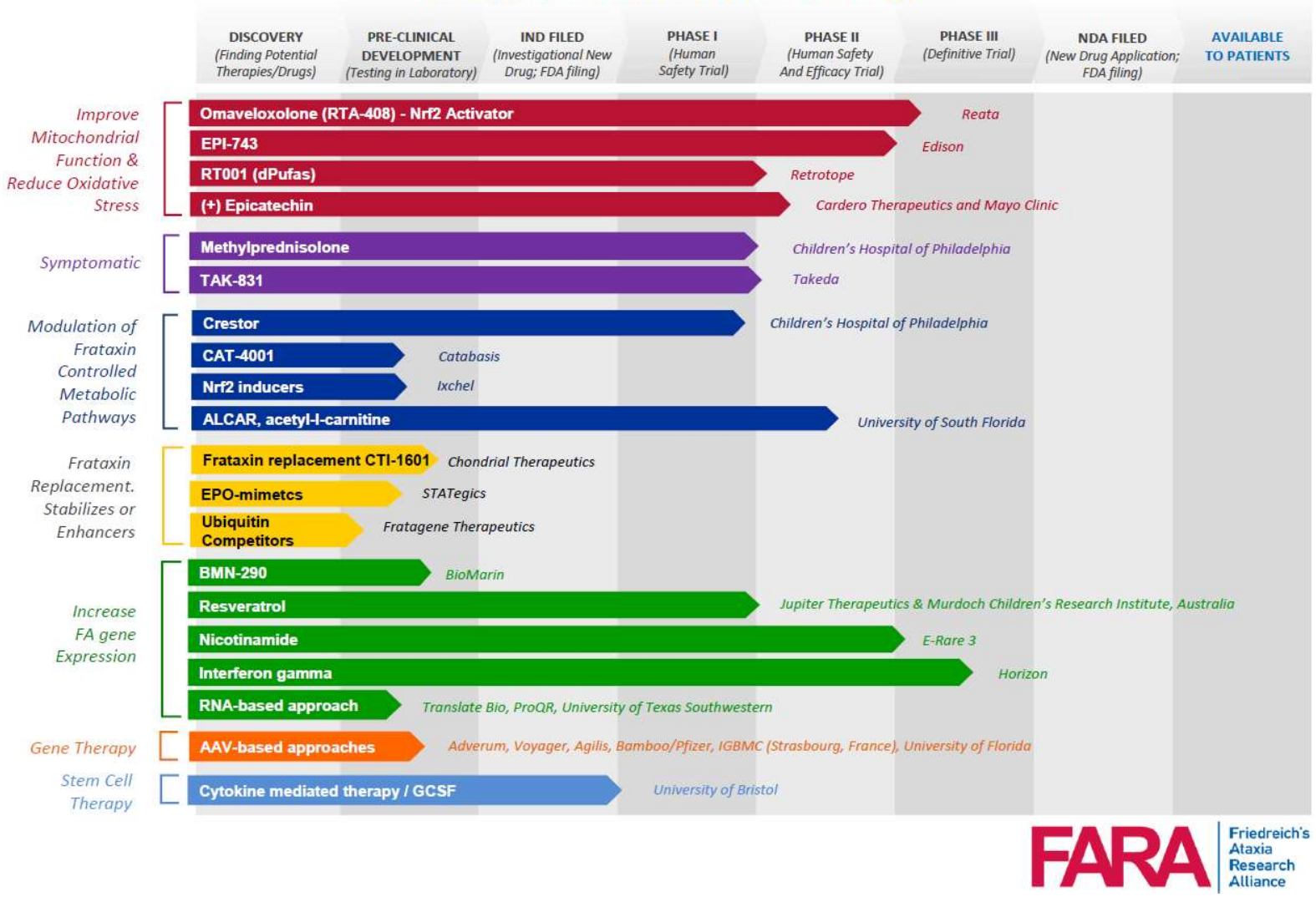
Friedreich ataxia



- Most common recessive ataxia (2 / 100,000)
- Intronic GAA expansion in *FXN* gene
- Typically:
  - onset 5-25 yrs
  - progressive ataxia
  - nystagmus < 50%
  - axonal neuropathy, distal atrophy, absent LL tendon reflexes
  - upgoing toes
  - MRI: cerebellar atrophy usually absent!
  - cardiomyopathy, diabetes, scoliosis, foot deformities

- Atypical phenotypes in 25 percent

FRIEDREICH'S ATAXIA TREATMENT PIPELINE



FARA Friedreich's Ataxia Research Alliance

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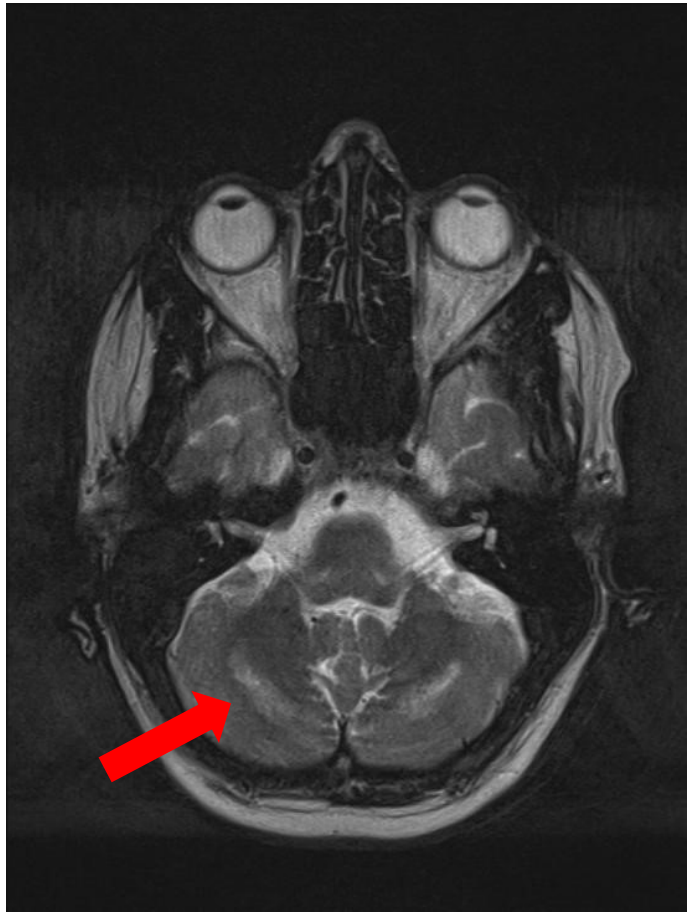
Table 5 Which autosomal recessive cerebellar ataxias to consider based on prominent features

Prominent clinical feature	First consider:
Peripheral neuropathy	FA, AVED, SANDO, AT, AOA1, AOA2
Spasticity	ARSACS, vLOFA, SPG7, CTX
Oculomotor apraxia	AT, ATLD, AOA1, AOA2
Oculocutaneous telangiectasias	AT
Retinitis pigmentosa	AVED
Chorea	AT, AOA1, AOA2
Dystonia	AT, AOA2
Seizures	ARCA2, IOSCA
Myopathy	MSS
Cataract	MSS
Mental retardation	AOA1, ARCA2, MSS

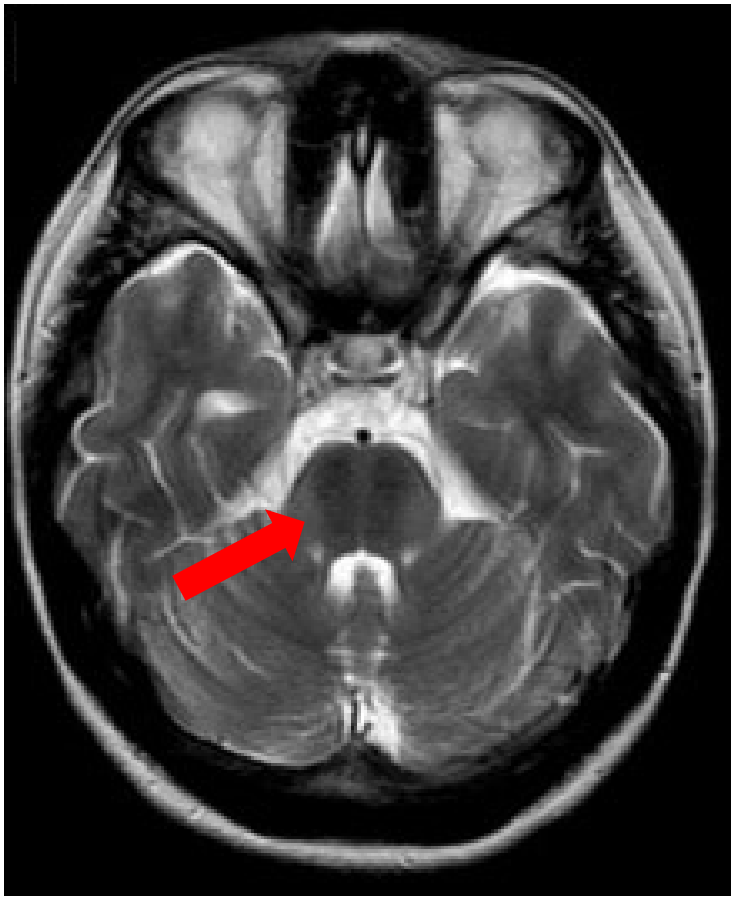
Vermeer S, et al. J Med Genet 2011

Additional ‘signatures’

- **MRI**



POLG



ARSACS

Additional ‘signatures’

- **MRI**

- **Biochemical markers**

- alpha-fetoprotein	Ataxia Telangiectasia, AOA2, AOA4
- vitamin E	Ataxia with vitamin E deficiency
- albumin, cholesterol	AOA1
- cholestanol, bile acids	Cerebrotendinous xanthomatosis
- oxysterols	Niemann-Pick type C
- Hex A/B	Tay Sachs, Sandhoff
- phytanic acid	Refsum

Diagnostic testing

1. check for expansions in Friedreich ataxia gene first

2. if available: NGS plus biochemical markers

New gene for CANVAS syndrome

- **C**erebellar **A**taxia, **N**europathy, **V**estibular **A**reflexia **S**yndrome
- Intronic bi-allelic AAGGG expansions in *RFC1* gene
- Already confirmed by other groups

New gene for CANVAS syndrome

- **C**erebellar **A**taxia, **N**europathy, **V**estibular **A**reflexia **S**yndrome
- Intronic bi-allelic AAGGG expansions in *RFC1* gene
- Already confirmed by other groups

- Mean age at onset: 58 years
- Preceding cough: 30%
- Sensory neuropathy: 100%
- Cerebellar ataxia: 78%
- Bilateral vestibulopathy: 74%
- Full-blown CANVAS: 65%

3 scenario’s based on family history

1. Dominant
2. Recessive
3. **Sporadic**

Etiological categories

Non-genetic cerebellar ataxia

a. acquired/symptomatic

b. degenerative

Genetic cerebellar ataxia

Acquired causes

- Structural lesions — *MRI*
- Medication
- Alcohol abuse
- Metabolic deficiencies — *vit E/B1/B12, TSH*
- Immune-mediated — *Antibody testing*
  - anti-GAD and perhaps others
  - gluten sensitivity

CNS Drugs
DOI 10.1007/s40263-014-0200-4

SYSTEMATIC REVIEW

Drug-Induced Cerebellar Ataxia: A Systematic Review

J. van Gaalen · F. G. Kerstens · R. P. P. W. M. Maas · L. Härmark · B. P. C. van de Warrenburg

In particular: antiepileptic drugs, benzodiazepines, and anti-cancer drugs

Number needed to harm for some <10

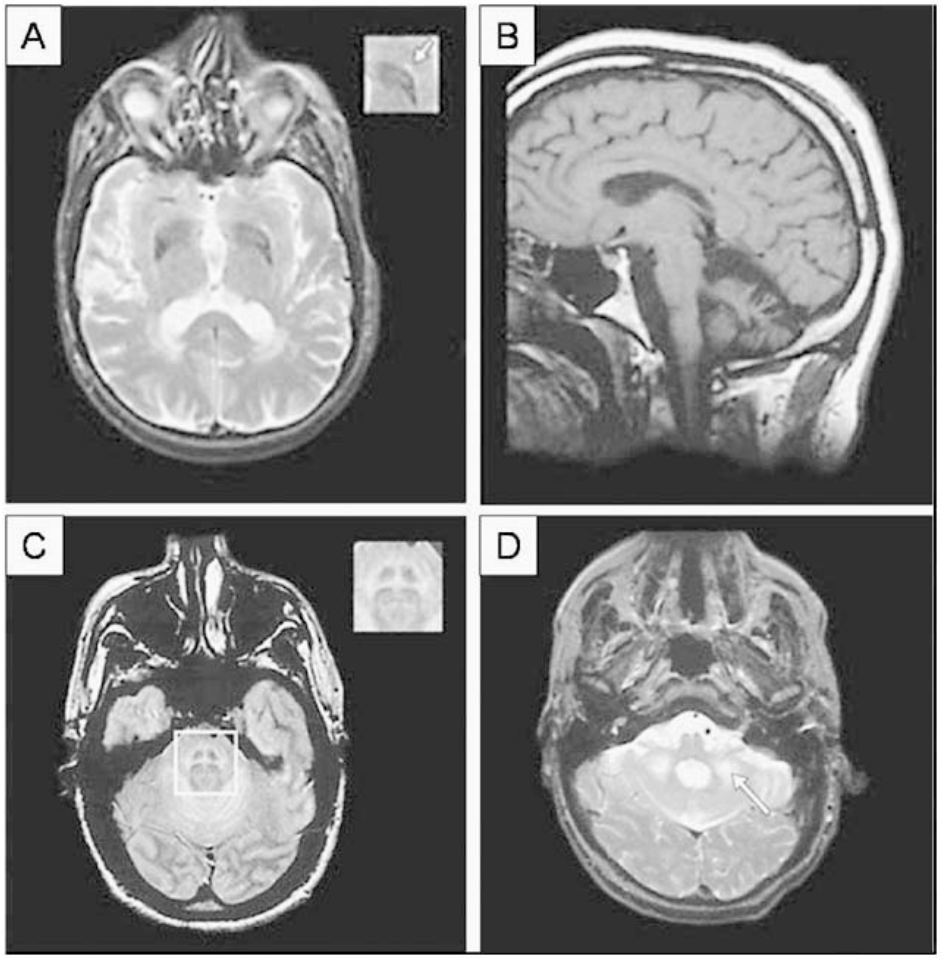
Can this be MSA-C?

Multiple system atrophy

- MSA-P vs. MSA-C (80 vs. 20%)
- Onset usually 50 – 60 years (but can be earlier!)
- Survival < 10 years
- Most important clue: (early) development of autonomic disturbances
- Gilman criteria (2008)
- Full-house phenotype:
  - parkinsonism, pyramidal signs
  - spontaneous sighs, RBD, cold hands/feet, stridor
  - polyminimyoclonus, axial dystonia (Pisa syndrome, antecollis)
  - high-pitched, quivery voice
- Abnormal structural or nuclear imaging

Possible MRI abnormalities

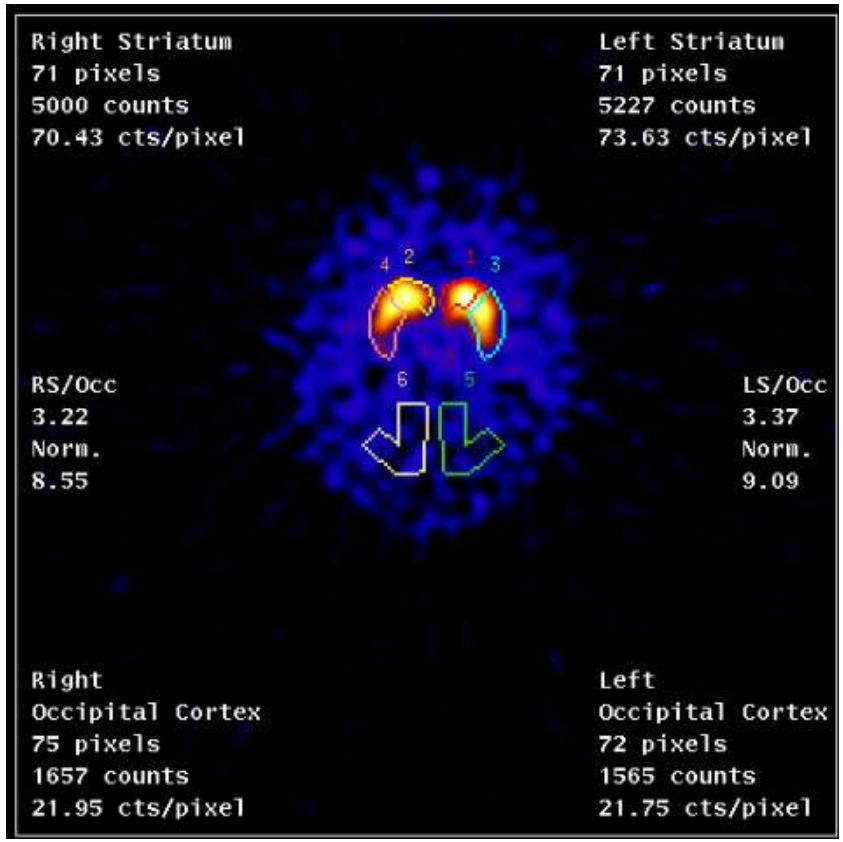
putaminal rim



cerebellar atrophy

hot cross bun sign

MCP sign



Abnormal DaT-SPECT in the absence of clinical parkinsonism

MSA-C

- Patients with sporadic, unexplained ataxia need to be followed up

- Only after 10 years is the development of MSA-C very unlikely

Can this still be genetic?

Yield of genetic testing

- Depends on onset age
- Examples from mixed cohorts:

SCA6 and Friedreich	5%
FXTAS	0-4% (men, onset > 50 yrs)
SCA2 and SCA3	1-2%
SPG7	1-2%

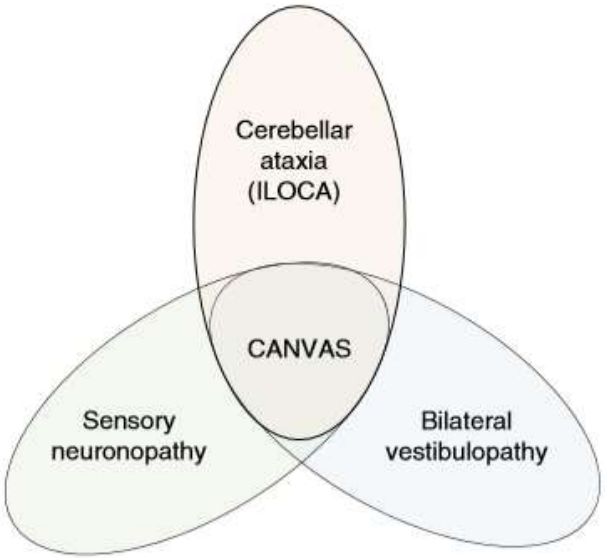
“MSA-C”

The clinical syndrome of MSA-C has a genetic differential!

- SCA17
- FXTAS
- and others

New gene for CANVAS syndrome

- **C**erebellar **A**taxia, **N**europathy, **V**estibular **A**reflexia **S**yndrome
- Intronic bi-allelic AAGGG expansions in *RFC1* gene
- Already confirmed by other groups
- **Sporadic cases!**
- Yield **22%** in late-onset ataxia
- If ataxia + neuropathy: 62%
- If CANVAS: 92%



So *RFC1* might be the most relevant gene for late-onset ataxia!

Current practice

- **All** — SCA1-2-3-6-7-17
  Friedreich ataxia
  RFC1 (particularly if CANVAS-like)
  SPG7
- **Onset < 50 yrs** — Biochemical markers
  NGS
- **Onset > 50 yrs** — FMR1 premutations in men (FXTAS)

Emerging practice

- **All**

  SCA1-2-3-6-7-17
  Friedreich ataxia
  RFC1 (particularly if CANVAS-like)
  +
  Biochemical markers
  NGS

- **Onset > 50 yrs**

  FMR1 premutations in men (FXTAS)

What remains?

Idiopathic early / late-onset cerebellar ataxia

- EOCA (onset < 50 years), ILOCA (onset > 50 years)
- Other causes ‘ruled out’
- Very frequent diagnoses
- Follow-up: developing into MSA-C?
- Etiology: mostly genetic / degenerative, some immune-mediated?

Therapy?

Some ataxias are treatable

- Removal of tumor
- Supplementing B12
- Immune modulating treatment
- Specific interventions for some metabolic ataxias

Some ataxias are treatable

- Removal of tumor
- Supplementing B12
- Immune modulating treatment
- Specific interventions for some metabolic ataxias

But most ataxias are not…..

Question 3

In a patient recently diagnosed with SCA3 … :

1. I do not have much to offer therapeutically
2. I would consider starting Riluzole
3. I would consider a referral to the rehabilitation unit
4. I would recommend intrathecal injection of mesenchymal stem cells

Lancet Neurol 2015; 14: 985–91

Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial

Silvia Romano, Giulia Coarelli, Christian Marcotulli, Luca Leonardi, Francesca Piccolo, Maria Spadaro, Marina Frontali, Michela Ferraldeschi, Maria Chiara Vulpiani, Federica Ponzelli, Marco Salvetti, Francesco Orzi, Antonio Petrucci, Nicola Vanacore, Carlo Casali, Giovanni Ristori

- Double-blind, placebo-controled RCT
- 12 months, 2dd 50 mg riluzole
- 60 patients: mainly SCA1, SCA2 and Freidreich
- Primary outcome: proportion patients with improvement SARA score ≥ 1 point
- 14/28 (50%) riluzole group versus 3/27 (11%) placebo group (OR 8.00, p 0.002)

Riluzole – comments and experience

- Only genetic ataxias in the trial
  - no SCA3 or SCA6 patients
- In our centre: reserved attitude, open discussion on pro's / con's
- A handful of patients treated, most have stopped (no effect, side effects), some stabilized, some improved
- European colleagues are not prescribing it, sceptic

J Neurol (2014) 261:251–258
DOI 10.1007/s00415-013-6910-6

REVIEW

The effectiveness of allied health care in patients with ataxia: a systematic review

Ella M. R. Fonteyn · Samyra H. J. Keus · Carla C. P. Verstappen · Ludger Schöls · Imelda J. M. de Groot · Bart P. C. van de Warrenburg

Rehabilitation

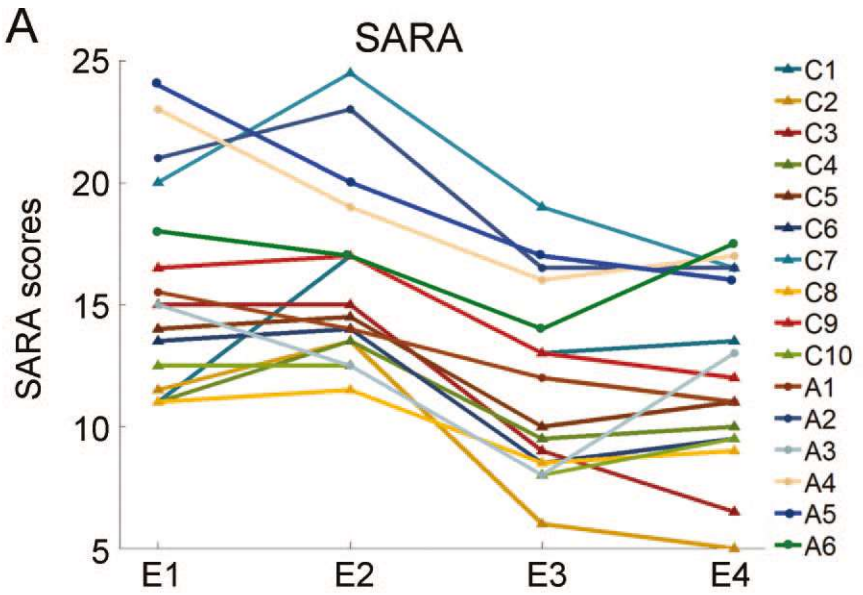
Physiotherapy

Exercise

Coordinative training

ARTICLES

Intensive coordinative training improves motor performance in degenerative cerebellar disease



Important points

- **First consider acquired causes of ataxia**
  - always if onset is acute/subacute
  - if slowly progressive: MRI plus limited set of blood tests
- **Enormous genetic heterogeneity**
  - NGS very suitable
  - but first rule out repeat expansions
  - test for (certain) genetic causes also in sporadic cases
- **MSA-C**
  - follow-up of at least 10 years needed
  - probable MSA-C still has a genetic differential
- **'Idiopathic' ataxia is frequent**
  - some immune-mediated?
- **Treatment often symptomatic**
  - 'training better than pills'
  - exciting developments

ePAG (European Patient Advocacy Groups) Voice

ePAGs Mission: Have the patient‘s voice heard

ePAGs role in ERN-RND: Highlight the problems specific to neurological illnesses that those affected have

For **contact details** of an ePAG representative visit:
http://www.ern-rnd.eu/about-us/#patientadvocates

Next milestone/need in this Disease Group: to incorporate all countries in EU irrespective of their economic status

Where ePAG Voice has been heard:

Diagnostic pathway should be shared with the person with Rare Disease (RD) even if undiagnosed

Care guidelines for RD should be available to all on line

Patient‘s opinion on what is important should be considered and incorporated as primary or secondary endpoint in clinical trials

Next challenge: Incorporation of patient registeries into European registeries for clinical trials

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Radboudumc

Joint webinar series

THANK YOU

Next Webinar: **Neuroacanthocytosis syndromes**

3 December 2019, 15-16h CET

Radboudumc