Paraparesi spastiche ereditarie

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- **Paraparesi Spastica** → sintomo/segno comune nella pratica clinica neurologica pediatrica (e non solo) causato da

✓ disturbi cerebrali acquisiti (ipossia cerebrale neonatale, infezioni sistemiche →paralisi cerebrale infantile)

✓ Disturbi strutturali, infettivi, demielinizzanti e metabolici

❑ Quali tappe diagnostiche?

- Raccolta dati anamnestici (familiarità, età d'esordio dei sintomi, progressione della malattia)
- Sintomi clinici caratteristici
- Esame obiettivo neurologico
- Esami neuroradiologici e relative diagnosi differenziali (con esami metabolici- biochimici – enzimatici)
- Altri esami diagnostici strumentali

❑ sintomi

- **Difficoltà progressiva di cammino dovuta a rigidità e debolezza progressive degli arti inferiori**

✓ *Difficoltà dell'equilibrio*
✓ *Tendenza ad inciampare, trascinare i piedi e ad incrociare le gambe*
✓ *Piede cavo, crampi muscolari, spasmi muscolari*

- Sintomi a decorso così lento da essere poco considerati dal soggetto ma notati dagli altri (familiari, amici…)
- Sintomi compaiono o all'inizio della deambulazione autonoma (o poco dopo) oppure anche tra le 2° e la 4° decade di vita, ma possono comparire ad ogni età
- Abilità atletiche durante l'infanzia (scarse performance o scarso interesse per lo sport: segni precoci della patologia)
- Nelle forme esordio infantile: ritardo delle tappe dello sviluppo motorio
- Nelle fasi più avanzate: mitto imperioso ed incontinenza urinaria

- Tenere però in considerazione come in forme complicate altri sintomi possono essere presenti:

✓ *Neuropatia periferica, epilessia, disturbi cutanei (ittiosi), atassia, neuropatia ottica, retinopatia, ritardo mentale, decadimento cognitivo, sordità, disturbi dell'eloquio, della masticazione e della deglutizione*

❑ esame obiettivo neurologico

- ✓ spasticità bilaterale degli arti inferiori
- ✓ ipostenia muscolare più evidente a livello di muscoli ileopsoas e del tibiale anteriore
- ✓ Alcuni soggetti manifestano la spasticità non associata a debolezza, mentre altri hanno spasticità e debolezza in egual misura
- ✓ Riflessi OT agli arti inferiori vivaci-policinetici e Risposta in estensione alla stimolazione cutanea plantare (segno di Babinski)

- ✓ Spesso modesto incremento dei riflessi OT agli arti superiori

→ coinvolgimento del tratto corticospinale

- ✓ Modesto deficit della sensibilità vibratoria e (meno frequente) di posizione

→ coinvolgimento fasci colonna dorsale

→altri segni di esame obiettivo neurologico

- Comune riscontro di :
  - Disturbi sfinterici (50%)
  - Piede cavo
  - Lieve dismetria distale

- Segni meno frequenti:
  - Paresi arti superiori
  - Amiotrofia distale

- Familiarità per disturbo simile che si adegua a modalità X-linked, AR e AD
  - **!!!!Attenzione se:**
  - Ipostenia > di spasticità
  - Atassia prominente
  - Amiotrofia prominente
  - Coinvolgimento arti superiori>arti inferiori
  - Neuropatia periferica
  - Asimmetria marcata
  - Alterazioni pigmentazione retinica
  - Segni extrapiramidali

→ Forme complicate? Altra patologia?

Diagnosi differenziale (1) :

- **Esordio infantile:**

Patologia	*Esame strumentale*
Paralisi cerebrale infantile (diplegia)	RMN encefalo, anamnesi neonatale
Malformazioni Strutturali (Malformazione di Arnold-Chiari; sublussazione atlo-occipitale)	RMN encefalo e midollo
Leucodistrofie (es, malattia di Krabbe) dosaggiE(galattocerebrosidasi)	RMN encefalo,
Malattie metaboliche (deficit di arginasi, abetalipoproteinaemia)	dosaggi Enzim. ,elettroforesi proteine
Distonia responsiva alla Levo-DOPA	terapia l-DOPA
Atassie spinocerebellari	**Ob. neurol.,analisi genetica**
Mielite (eziologia infettiva)	esame liquorale
Sclerosi Multipla	RMN encefalo, esame liquorale

- **Diagnosi differenziale (2) :**

- **Esordio adulto:**

Patologia	*Esame strumentale*
malattie degenerative cervicali	RMN midollo
Sclerosi multipla	RMN encefalo e midollo-liquor
Malattia del Motoneurone	EMG/ENG
Neoplasie	RMN encefalo e midollo
Mieliti (eziologia infettiva)	liquor
Malformazioni arterovenose durali	RMN-Angiografia
Malformazione di Arnold-Chiari	RMN encefalo e midollo
Adrenoleucodistrofia	RMN encefalo, dosaggio VLCFA
Atassie spinocerebellari	**Ob. neurol.,analisi genetica**
Deficit di vitamina B12 e Vitamina E	dosaggi Vit B12 e Vit E
Latirismo	intossicazione da *latyrus sativus* cicerchie
Distonia responsiva alla Levo-DOPA	risposta ad L-DOPA
Infezioni (sifilide, HIV, Virus leucemia a cell T tipo 1)	analisi siero e liquor
Deficit di rame	dosaggio rame e ceruloplasmina

Escluse patologie precedentemente indicate in base a dati anamnestici, valutazione obiettiva ed esami strumentali e biochimici

Ipotesi di paraparesi spastica ereditaria

❑HSP ed Esami Strumentali

- RMN midollo: sottile senza grossolane anomalie (assottigliamento in particolare del midollo spinale cervicale e dorsale)
- RMN encefalo: diversi casi di atrofia od assottigliamento corpo calloso; alterazioni della sostanza bianca (patchy demyelination)
- DTI (diffusion tensor imaging; integrità di microstruttura SB) può mostrare alterazioni precoci nella fibra nervosa in paz con mutaz SPG4 (Duning et al, 2010)
- Potenziali evocati motori: non evocabili o rallentati agli arti inferiori, normali arti superiori
- PESS: piccoli o assenti, arti inferiori più coinvolti di superiori
- EMG ed ENG: normali in più parte HSP; alcune forme associate a neuropatia assonale/demielinizzante
- Esame liquor: non significativo
- Analisi genetica: considerare ereditarietà, età d'esordio, forma pura/complicata

Paraparesi spastiche ereditarie (HSP)

- ✓ **Gruppo di disordini neurologici ereditari rari ed eterogenei (identificate più di 70 forme).**

- ✓ **Primi sintomi: progressiva «spasticità» agli arti inferiori ed «ipostenia» di muscolatura degli arti inferiori e del bacino [insidioso]**

- ✓ **Ereditarietà:** circa 70 geni identificati
- ***Autosomica DOMINANTE: 70-80% di tutte HSP in popolazione occidentale***
- ***Autosomica RECESSIVA: 20-30%***
- ***X-linked : molto rara***

- ✓ Incidenza di 1:20000 (negli USA)
- ✓ Prevalenza: sia per forme autosomiche dominanti che recessive
  1.8 /100000- altri report 4,3-9,8 : 100000

- ✓ **Divise in 1) forme «pura» / «non complicata» e 2) forma «complessa»/ «complicata»**
- ✓ **Diversi modi di identificare «questa malattia»: Paraparesi spastica ereditaria, paraparesi spastica familiare, Malattia di Strumpell-Lorrain……**

❖ *Forme pure*

- Disturbo neurologico limitato a spasticità progressiva agli arti inferiori , disturbi dello sfintere urinario, modesta riduzione della sensibilità vibratoria e statochinestesica (di posizione) [Harding 1983].

- Esordio ad ogni età, dalla prima infanzia alla tarda età adulta
- Lenta progressione negli anni, senza acuzie/remissioni/periodi di importanti peggioramenti
- progressive difficoltà di cammino che possono portare a necessità di ausili (canadesi, deambulatori, carrozzina)
- Ipostenia di specifici gruppi muscolari (musc prossimali arti inferiori,o distale arti inf –TA)
- In forme ad esordio infantile, a volte , sintomi peggiorano fino all'adolescenza poi si stabilizzano , con mantenimento del cammino con ausili

- Conservata la stenia e la coordinazione agli arti superiori
- Assente coinvolgimento di eloquio, masticazione o deglutizione.
- *Non modifica durata di vita (???)*

❖ *Forme Complesse*

- spasticità progressiva agli arti inferiori, ipostenia arti inf. disturbi dello sfintere urinario, modesta riduzione della sensibilità vibratoria e statochinestesica (di posizione)

+

- Epilessia, ritardo cognitivo, demenza, amiotrofia, neuropatia periferica, coinvolgimento del sistema extrapiramidale e cerebellare, retinopatia, neuropatia ottica, sordità
- Molte forme di HSP complesse sono associate ad atrofia muscolare distale simmetrica di arti superiori ed inferiori

[Refsum & Skillicorn 1954, Gilman & Horenstein 1964, Silver 1966, Neuhauser et al 1976, Sack et al 1978, Abdallat et al 1980, Heijbel & Jagell 1981, Bahemuka & Brown 1982, Joshita et al 1982, Fujii et al 1986, Uyama et al 1988, Costeff et al 1989, Serena et al 1990, Antinolo et al 1992, Farag et al 1994, Thomas et al 1994, Meierkord et al 1997].

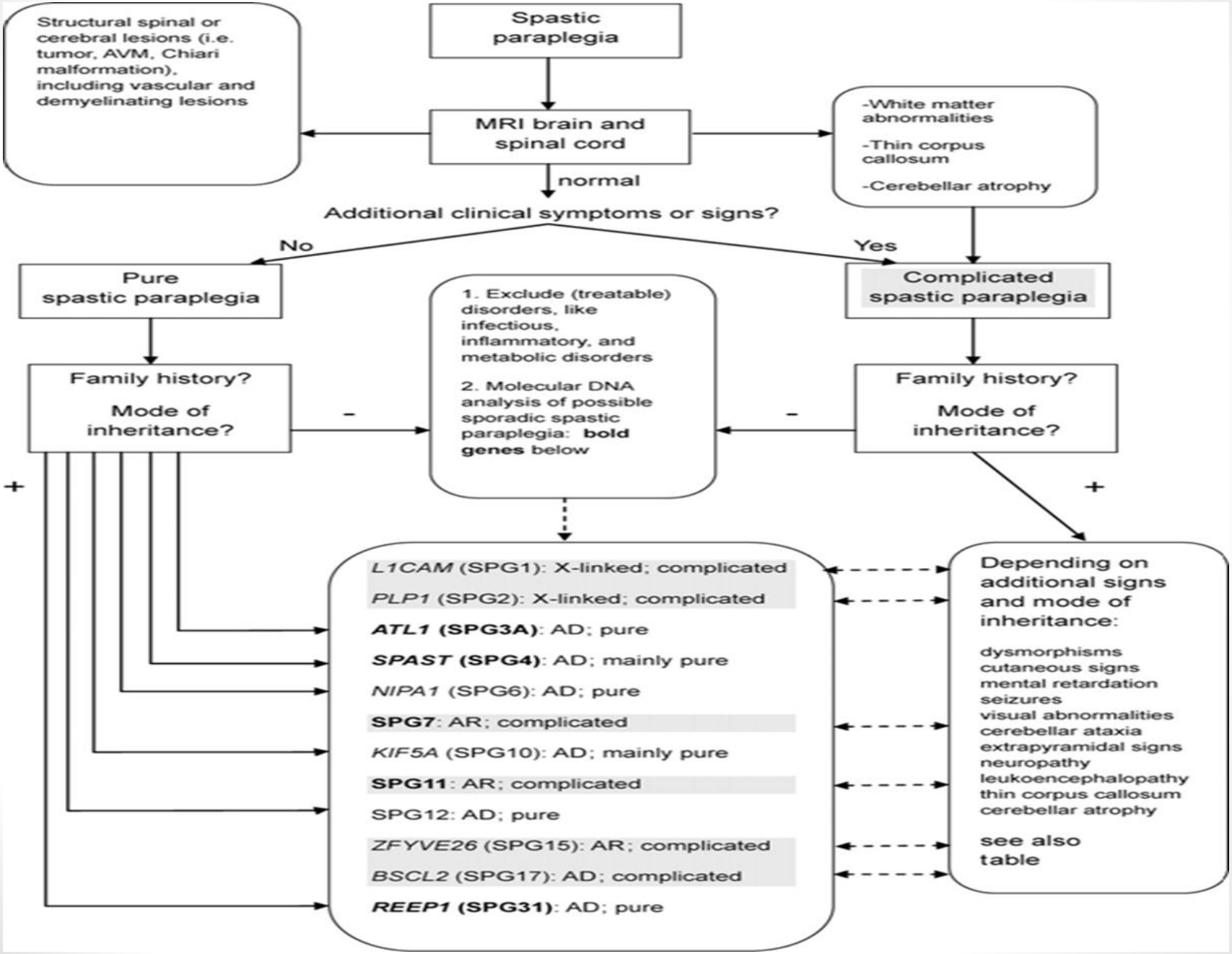
❑ paraparesi spastica (apparentemente sporadica)

Molti individui con tutti i segni e sintomi di una HSP non hanno altri membri della famiglia affetti

- Le forme recessive e quelle legate al crom X possono «saltare» le generazioni→ la malattia può «passare» inosservata per generazioni e «comparire all'improvviso».
- Età d'esordio , progressione e gravità sono molto variabili → malattia passa inosservata nelle generazioni precedenti o un individuo affetto è deceduto prima della comparsa dei sintomi

- Estrema eterogeneità genetica, variabilità di penetranza
- Next generation sequencing : identificazione di > 70 geni con altrettanti sottotipi clinici

algoritmo diagnostico



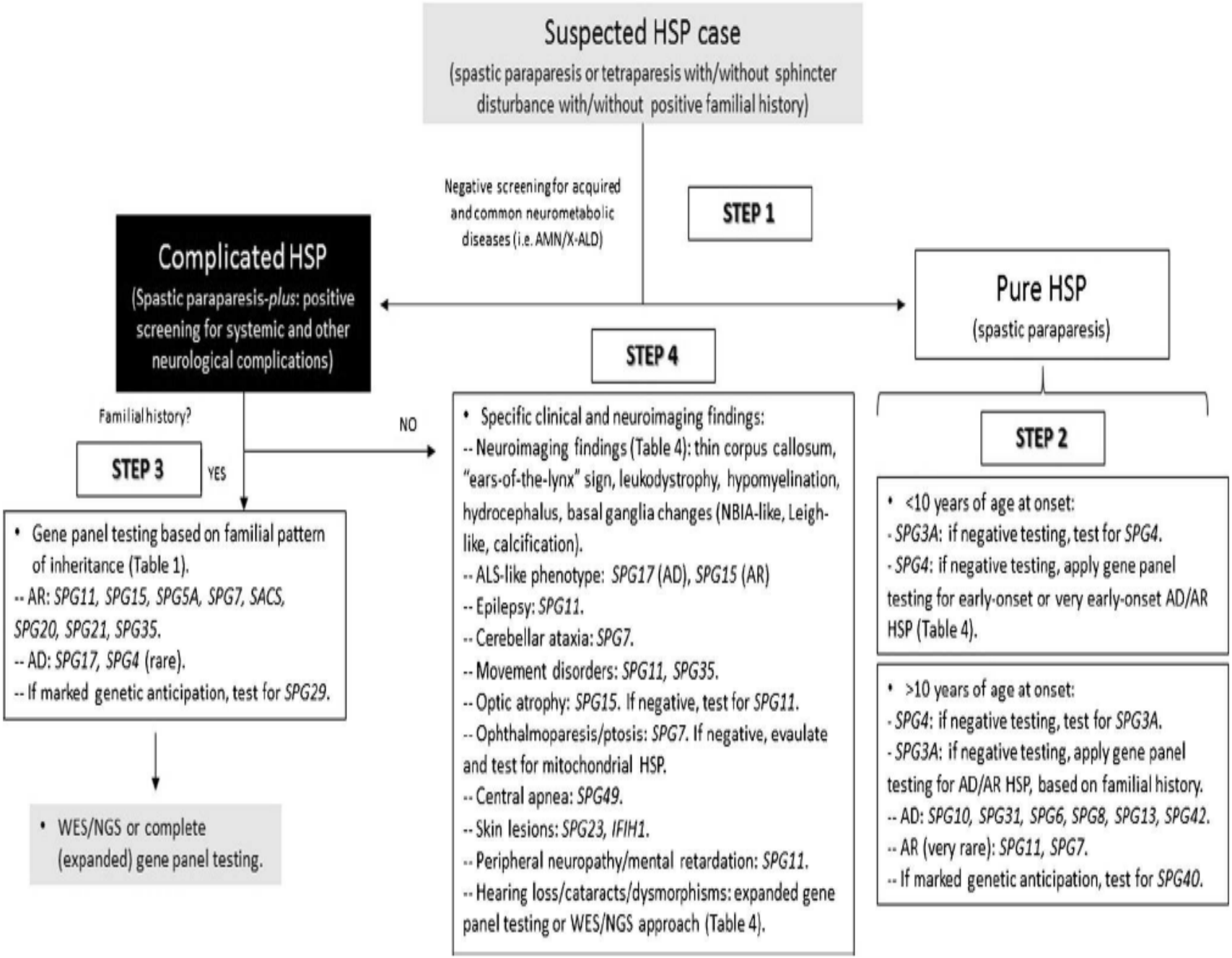

Suspected HSP case
(spastic paraparesis or tetraparesis with/without sphincter disturbance with/without positive familial history)
Negative screening for acquired and common neurometabolic diseases (i.e. AMN/X-ALD)
STEP 1
Complicated HSP
(Spastic paraparesis-plus: positive screening for systemic and other neurological complications)
Pure HSP
(spastic paraparesis)
STEP 4
Familial history?
NO
STEP 3
YES
• Specific clinical and neuroimaging findings:
-- Neuroimaging findings (Table 4): thin corpus callosum, "ears-of-the-lynx" sign, leukodystrophy, hypomyelination, hydrocephalus, basal ganglia changes (NBIA-like, Leigh-like, calcification).
-- ALS-like phenotype: SPG17 (AD), SPG15 (AR)
-- Epilepsy: SPG11.
-- Cerebellar ataxia: SPG7.
-- Movement disorders: SPG11, SPG35.
-- Optic atrophy: SPG15. If negative, test for SPG11.
-- Ophthalmoparesis/ptosis: SPG7. If negative, evaulate and test for mitochondrial HSP.
-- Central apnea: SPG49.
-- Skin lesions: SPG23, IFIH1.
-- Peripheral neuropathy/mental retardation: SPG11.
-- Hearing loss/cataracts/dysmorphisms: expanded gene panel testing or WES/NGS approach (Table 4).
STEP 2
• <10 years of age at onset:
- SPG3A: if negative testing, test for SPG4.
- SPG4: if negative testing, apply gene panel testing for early-onset or very early-onset AD/AR HSP (Table 4).
• >10 years of age at onset:
- SPG4: if negative testing, test for SPG3A.
- SPG3A: if negative testing, apply gene panel testing for AD/AR HSP, based on familial history.
-- AD: SPG10, SPG31, SPG6, SPG8, SPG13, SPG42.
-- AR (very rare): SPG11, SPG7.
-- If marked genetic anticipation, test for SPG40.
• Gene panel testing based on familial pattern of inheritance (Table 1).
-- AR: SPG11, SPG15, SPG5A, SPG7, SACS, SPG20, SPG21, SPG35.
-- AD: SPG17, SPG4 (rare).
-- If marked genetic anticipation, test for SPG29.
• WES/NGS or complete (expanded) gene panel testing.

Table 1 Classification of hereditary spastic paraplegia and the main subtypes [1–3, 10, 11]

Classification of hereditary spastic paraplegia	
Harding's classification, based on signs and symptoms	
Pure (or uncomplicated) HSP	Spastic paraparesis with sphincteral disturbances and mild to moderate sensory loss
Complicated (or complex) HSP	Spastic paraparesis *plus* (additional neurological and systemic signs and symptoms)
Harding's classification, based on age at onset of spasticity	
HSP type I	Early onset: starting before 35 years of age
HSP type II	Classical: starting after 35 years of age
Based on the pattern of inheritance	
Autosomal dominant HSP	SPG3A, SPG4, SPG6, SPG8, SPG9, SPG10, SPG12, SPG13, SPG17, SPG19, SPG29, SPG31, SPG33, SPG36, SPG37, SPG38, SPG41, SPG42, SPG72, SPG73
Autosomal recessive HSP	SPG5, SPG7, SPG11, SPG14, SPG15, SPG18, SPG20, SPG21, SPG23, SPG24, SPG25, SPG26, SPG27, SPG28, SPG30, SPG32, SPG35, SPG39, SPG43, SPG44, SPG45/SPG65, SPG46, SPG47, SPG48, SPG49, SPG50, SPG51, SPG52, SPG53, SPG54, SPG55, SPG56, SPG57, SPG58, SPG59, SPG60, SPG61, SPG62, SPG63, SPG64, SPG66, SPG67, SPG68, SPG69, SPG70, SPG71, SPG72, SPG74
X-linked HSP	SPG1, SPG2, SPG16, SPG22, SPG34
Mitochondrial HSP	*MT-ATP6*, *MT-TI*, *MT-CO3*, *MT-ND4*
Based on intracellular pathophysiological mechanisms	
Membrane trafficking and organelle shaping	SPG3A, SPG4, SPG6, SPG11, SPG15, SPG18, SPG20, SPG31, SPG59, SPG60, SPG61, SPG62, SPG69, SPG72
Axonal transport	SPG4, SPG10, SPG30, SPG58
Mitochondrial dysfunction	SPG7, SPG20, SPG31
Lipid metabolism disturbances	SPG5, SPG26, SPG28, SPG35, SPG39, SPG46, SPG54, SPG56
Myelination abnormalities	SPG1, SPG2, SPG39, SPG42, SPG67

Sgobbi de Souza, Cerebellum 2017

Table 3 Main clinical and neuroimaging findings of each hereditary spastic paraplegia (HSP) subtype

HSP subtype (*gene*; locus)	Clinical and neuroimaging findings
SPG1 (*L1CAM*; Xq28)	XLR; Gareis–Mason syndrome; MASA syndrome, CRASH syndrome; hydrocephalus, agenesis of the corpus callosum
SPG2 (*PLP1*; Xq22.2)	XLR; nystagmus, optic atrophy, severe hypomyelination
SPG3A (*ATL1*; 14q22.1)	AD; rarely optic atrophy, seizures and thin corpus callosum
SPG4 (*SPAST*; 2p22.3)	AD; classical Strümpell–Lorrain disease
SPG5A (*CYP7B1*; 8q12.3)	AR; cerebellar ataxia, spastic ataxia, optic atrophy
SPG6 (*NIPA1*; 15q11.2)	AD; postural tremor, seizures
SPG7 (*SPG7*; 16q24.3)	AR; cerebellar ataxia, chronic progressive external ophthalmoplegia, cerebellar atrophy
SPG8 (*KIAA0196*; 8q24.13)	AD; lower limb distal amyotrophy
SPG9A (*ALDH18A1*; 10q24.1)	AD; CMNSS, SPACGR, cerebellar ataxia, ALS-like
SPG9B (*ALDH18A1*; 10q24.1)	AR; facial dysmorphism, tremor, mental retardation, microcephaly, atrophy of the corpus callosum
SPG10 (*KIF5A*; 12q13.3)	AD; rarely with Parkinsonism, cerebellar ataxia, neuropathy, distal amyotrophy, cognitive decline
SPG11 (*SPG11*; 15q21.1)	AR; cerebellar ataxia, mental retardation, parkinsonism, distal amyotrophy, maculopathy, thin corpus callosum, "ears-of-the-lynx" sign, mild white matter changes
SPG12 (*RTN2*; 19q13.32)	AD; classical pure HSP
SPG13 (*HSPD1*; 2q33.1)	AD; classical pure HSP, marked spasticity
SPG14 (3q27-q28)	AR; distal motor neuropathy, mental retardation
SPG15 (*ZFYVE26*; 14q24.1)	AR; Kjellin syndrome, distal amyotrophy, hearing loss, retinal degeneration, neuropathy, psychosis, cerebellar ataxia, levodopa-responsive Parkinsonism, epilepsy; thin corpus callosum, mild white matter changes
SPG16 (Xq11.2-q23)	XLR; motor aphasia, mental retardation, maxillary hypoplasia, short and thick distal phalanges
SPG17 (*BSCL2*; 11q12.3)	AD; Silver syndrome, ALS-like phenotype, prominent thenar and interossei musculature wasting
SPG18 (*ERLIN2*; 8p11.23)	AR; severe spasticity, seizures, mental retardation, multiple joint contractures
SPG19 (9q)	AD; mild neuropathy
SPG20 (*SPG20*; 13q13.3)	AR; Troyer syndrome, multiple dysmorphisms, distal amyotrophy; rarely cerebellar ataxia, tongue dyspraxia, cerebellar atrophy, mild white matter changes
SPG21 (*ACP33*; 15q22.31)	AR; MAST syndrome, cognitive decline, extrapyramidal and cerebellar signs, neuropathy, thin corpus callosum, frontotemporal atrophy
SPG22 (*SLC16A2*; Xq13.2)	XLSD; cerebellar ataxia, mental retardation, dystonia, typical dysmorphisms, hypomyelinating leukodystrophy
SPG23 (2q24-q32)	AR; Lison syndrome, patchy vitiligo, hyperpigmentation of exposed areas, lentigenes, facial features, mental retardation, mild neuropathy
SPG24 (13q14)	AR; pure HSP
SPG25 (6q23.3-q24.1)	AR; "familial intervertebral disk disease"
SPG26 (*B4GALNT1*; 12p11.1-q14)	AR; mental retardation, neuropathy, distal amyotrophy, cerebellar ataxia, nystagmus, dystonia, dyskinesias
SPG27 (10q22.1-q24.1)	AR; typical pure HSP
SPG28 (*DDHD1*; 14q22.1)	AR; typical pure HSP
SPG29 (1p31.1-p21.1)	AD; hearing loss, genetic anticipation, hiatal hernia
SPG30 (*KIF1A*; 2q37.3)	AR; mild neuropathy, mild cerebellar ataxia, mild cerebellar atrophy
SPG31 (*REEP1*; 2p11.2)	AD; distal amyotrophy
SPG32 (14q12-q21)	AR; mild mental retardation
SPG33 (*ZFYVE27*; 10q24.2)	AD; pure HSP
SPG34 (Xq24-q25)	XLR; Brazilian family, pure HSP

Table 3 (continued)

HSP subtype (*gene*; locus)	Clinical and neuroimaging findings
SPG35 (*FA2H*; 16q23.1)	AR; FAHN syndrome, cognitive decline, cerebellar ataxia, dystonia, optic atrophy, leukodystrophy, brain iron accumulation; rarely strabismus and seizures
SPG36 (12q23-q24)	AD; neuropathy
SPG37 (8p21.1-q13.3)	AD; pure HSP
SPG38 (4p16-p15)	AD; ALS-like phenotype, Silver syndrome-like
SPG39 (*PNPLA6*; 19p13.2)	AR; Troyer syndrome-like, marked distal amyotrophy, cerebellar and thoracic spinal cord atrophy
SPG40 (unknown)	AD; pure HSP, genetic anticipation
SPG41 (11p14.1-p11.2)	AD; pure HSP
SPG42 (*SLC33A1*; 3q25.31)	AD; pure HSP
SPG43 (*C19ORF12*; 19q12)	AR; Malian and Brazilian families, severe amyotrophy, multiple contractures
SPG44 (*GJC2*; 1q42.13)	AR; cerebellar ataxia, mental retardation, hearing loss, seizures, painful spasms, thin corpus callosum, hypomyelinating leukodystrophy
SPG45/SPG65 (*NT5C2*; 10q24.32-q24.33)	AR; mental retardation, optic atrophy, joint contractures, strabismus, nystagmus, dysplastic corpus callosum, white matter changes
SPG46 (*GBA2*; 9p13.3)	AR; cerebellar ataxia, mental retardation, head tremor, congenital cataracts, hearing loss, small testicles, cerebellar atrophy, thin corpus callosum
SPG47 (*AP4B1*; 1p13.2)	AR; neonatal hypotonia, mental retardation, dysmorphisms, stereotypic laughter, shy character, spastic tongue protrusion, dystonia, late-onset febrile seizures, thin corpus callosum, white matter changes
SPG48 (*AP5Z1*; 7p22.1)	AR; pure HSP, mild cervical spine hyperintensities
SPG49 (*TECPR2*; 14q32.31)	AR; mental retardation, cerebellar ataxia, complicated gastroesophageal reflux, recurrent respiratory infections, dysmorphisms, recurrent central apnea, seizures, thin corpus callosum, cerebellar atrophy
SPG50 (*AP4M1*; 7q22.1)	AR; neonatal hypotonia, mental retardation, strabismus, dysmorphisms, infantile-onset seizures, ventriculomegaly, thin corpus callosum, white matter changes
SPG51 (*AP4E1*; 15q21.2)	AR; neonatal hypotonia, mental retardation, short stature, dysmorphisms, shy character, stereotypic laughter, seizures, nystagmus, joint contractures, marked leukodystrophy, ventriculomegaly, cerebellar atrophy
SPG52 (*AP4S1*; 14q12)	AR; neonatal hypotonia, mental retardation, joint contractures, smiling attitude, shy character, dysmorphisms
SPG53 (*VPS37A*; 8p22)	AR; mental retardation, dystonia, pectus carinatum, hypertrichosis
SPG54 (*DDHD2*; 8p11.23)	AR; mental retardation, joint contractures, dysmorphisms, strabismus, optic nerve hypoplasia, thin corpus callosum, white matter changes, abnormal lipid peaks
SPG55 (*C12ORF65*; 12q24.31)	AR; progressive visual loss, optic atrophy, strabismus, distal neuropathy, mental retardation, mild facial dysmorphisms, hypoplastic corpus callosum
SPG56 (*CYP2U1*; 4q25)	AR; neuropathy, dystonia, mental retardation, white matter changes, thin corpus callosum, basal ganglia calcification
SPG57 (*TFG*; 3q12.2)	AR; optic atrophy, neuropathy, contractures
SPG58 (*KIF1C*; 17p13.2)	AR; cerebellar ataxia, hypodontia, mental retardation, microcephaly, short stature, fragmentary clonus, chorea, white matter changes
SPG59 (*USP8*; 15q21.2)	AR; pure HSP
SPG60 (*WDR48*; 3p22.2)	AR; nystagmus, neuropathy
SPG61 (*ARL6IP1*; 16p12.3)	AR; severe neuropathy, severe mutilating acropathy
SPG62 (*ERLIN1*; 10q24.31)	AR; cerebellar ataxia, distal amyotrophy
SPG63 (*AMPD2*; 1p13.3)	AR; short stature, white matter changes, thin corpus callosum
SPG64 (*ENTPD1*; 10q24.1)	AR; mental retardation, microcephaly, delayed puberty, mild white matter changes

Table 3 (continued)

HSP subtype (*gene*; locus)	Clinical and neuroimaging findings
SPG66 (*ARSI*; 5q32)	AR; severe neuropathy, thin corpus callosum, colpocephaly, cerebellar hypoplasia
SPG67 (*PGAP1*; 2q33.1)	AR; global developmental delay, hand tremor, agenesis of the corpus callosum, cerebellar vermis hypoplasia, hypomyelination
SPG68 (*FLRT1*; 11q13.1)	AR; mild amyotrophy, nystagmus, optic atrophy; without marked spasticity
SPG69 (*RAB3GAP2*; 1q41)	AR; mental retardation, deafness, cataracts
SPG70 (*MARS*; 12q13.3)	AD; mild mental retardation, nephrotic syndrome
SPG71 (*ZFR*; 5p13.3)	AR; pure HSP, thin corpus callosum
SPG72 (*REEP2*; 5q31.2)	AR/AD; postural tremor
SPG73 (*CPT1C*; 19q13.33)	AD; mild amyotrophy
SPG74 (*IBA57*; 1q42.13)	AR; neuropathy, optic atrophy
IAHSP (*ALS2*; 2q33.1)	AR; ascending phenotype, marked pyramidal hypersignal
SPOAN (*KLC2*; 11q13.2)	AR; Brazil, Egypt; nystagmus, optic atrophy, hyperhidrosis, marked acoustic startle reflex, distal amyotrophy, neuropathy; Parkinsonism; mild spine atrophy
CPSQ-I (*GAD1*; 2q31.1)	AR; mental retardation, occasional seizures, microcephaly, multiple contractures
Spastic paraplegia with deafness	XL; tremor, cataracts, deafness, short stature, hypogonadism
BICD2-associated HSP (9q22.31)	AR; amyotrophy
CCT5-associated HSP (5p15.2)	AR; Cavanagh variant, severe neuropathy, mutilating acropathy, vagal hyperactivity, mild spine atrophy
FAM134B-associated HSP (5p15.1)	AR; painless neuropathy, mutilating acropathy, hyperhidrosis
EXOSC3-associated HSP (9p13.2)	AR; short stature, mental retardation, cerebellar ataxia, strabismus, distal amyotrophy, tongue atrophy, adducted thumbs, cerebellar atrophy, enlarged cisterna magna
LYST-associated HSP (1q42.3)	AR; cerebellar ataxia, neuropathy, thoracic spine and cerebellar atrophy
GRID2-associated HSP (4q22.1-q22.2)	AR; cerebellar ataxia, frontotemporal dementia, lower motor neuron syndrome, ALS-like phenotype, cerebellar atrophy
IFIH1-related HSP (2q24.2)	AD; British families, multisystem inflammatory disorders
ADAR1-related HSP (1q21.3)	AD; pure HSP, high interferon-1 levels
RNASEH2B-related HSP (13q14.3)	AD; pure HSP, unspecific white matter changes
KLC4-associated HSP (6p21.1)	AR; joint contractures, marked pyramidal tract hypersignal, thin corpus callosum, white matter changes, cerebellar atrophy, dentate nucleus hypersignal
PMCA4-associated HSP (1q32.1)	AD; Chinese families, pure HSP
MAG-associated HSP (19q13.12)	AR; mental retardation, cerebellar ataxia, amyotrophy
TUBB4A-related HSP (19p13.3)	AR; cerebellar ataxia, hypomyelinating leukodystrophy
FARS2-associated HSP (6p25.1)	AR; pure HSP
DNM2-associated HSP (19p13.2)	AD; pure HSP
MT-CO3 gene mutations	Mitochondrial; mental retardation, ophthalmoplegia, severe lactic acidosis, Leigh-like features, COX deficiency
MT-TI gene mutations	Mitochondrial; cerebellar ataxia, mental retardation, chronic progressive external ophthalmoplegia; normal muscle biopsy; cardiomyopathy, hearing loss, diabetes
MT-ND4 gene mutations	Mitochondrial; visual loss (Leber-like)
MT-ATP6 gene mutations	Mitochondrial; neuropathy, normal lactate, normal muscle biopsy

Table 4 Clinical and neuroimaging parameters in the differential diagnosis process of hereditary spastic paraplegia (HSP)

Clinical and neuroimaging parameters	Differential diagnosis of HSP
Complicated HSP	SPG1, SPG2, SPG3A*, SPG4*, SPG5A*, SPG6*, SPG7, SPG9A, SPG9B, SPG10*, SPG11, SPG14, SPG15, SPG16, SPG17*, SPG18, SPG20, SPG21, SPG22, SPG23, SPG26, SPG29, SPG30*, SPG32, SPG35, SPG36*, SPG38, SPG39*, SPG43, SPG44, SPG45/SPG65, SPG46, SPG47, SPG49, SPG50, SPG51, SPG52, SPG53, SPG54, SPG55, SPG56, SPG57, SPG58, SPG59, SPG60, SPG61, SPG62, SPG63, SPG64, SPG66, SPG67, SPG68, SPG69, SPG70, SPG74, SPOAN, CPSQ-I, Spastic paraplegia with deafness, *FAM134B*, *CCT5*, *EXOSC3*, *LYST*, *GRID2*, *IFIH1*, *KLC4*, *MAG*, *TUBB4A*, *MT-CO3*, *MT-TI*, *MT-ATP6*, *MT-ND4*
Pure HSP	SPG3A, SPG4, SPG5A, SPG6, SPG7*, SPG8, SPG10, SPG12, SPG13, SPG16, SPG17, SPG19, SPG24, SPG25, SPG27, SPG28, SPG30, SPG31, SPG33, SPG34, SPG36, SPG37, SPG39, SPG40, SPG41, SPG42, SPG43*, SPG48, SPG59, SPG71, SPG72, SPG73, IAHSP, *BICD2*, *ADAR1*, *RNASEH2B*, *PMCA4*, *FARS2*, *DNM2*
Early onset HSP (juvenile or late childhood onset)	SPG3A, SPG4, SPG5A, SPG6, SPG9A, SPG10, SPG12, SPG13, SPG14*, SPG17, SPG18, SPG20, SPG21*, SPG22, SPG23, SPG24, SPG26, SPG28, SPG29, SPG30, SPG31, SPG32, SPG34, SPG35, SPG37*, SPG39, SPG42, SPG43, SPG44, SPG45/SPG65, SPG46, SPG47, SPG49, SPG53, SPG54, SPG55, SPG56, SPG57, SPG58, SPG59, SPG60, SPG61, SPG62, SPG63, SPG64, SPG65, SPG66, SPG67, SPG68, SPG69, SPG70, SPG71, SPG72, SPG74, CPSQ-I, Spastic paraplegia with deafness, *CCT5*, *FAM134B*, *EXOSC3*, *IFIH1*, *ADAR1*, *KLC4*, *PMCA4*, *TUBB4A*, *FARS2*, *DNM2*, *MT-CO3*
Very early onset HSP (infant, early childhood, or neonatal onset)	SPG1, SPG2, SPG3A*, SPG4*, SPG16, SPG22, SPG24, SPG45/SPG65, SPG47, SPG50, SPG51, SPG52, SPG60, SPG61, SPG63, SPG66, SPG69, SPG70, SPG71, SPG72, IAHSP, SPOAN, *BICD2*, *CCT5*, *RNASEH2B*, *FARS2*

Leukodystrophy	SPG4*, SPG5A*, SPG7, SPG9B*, SPG11, SPG15*, SPG20, SPG35, SPG45/SPG65, SPG47, SPG50, SPG51, SPG54, SPG56, SPG58, SPG63, SPG64*, *RNASEH2B*, *KLC4*
Hypomyelination	SPG2, SPG22, SPG44, SPG67, *TUBB4A*
Thin corpus callosum (including agenesis, hypoplasia or dysgenesis)	SPG1, SPG3A*, SPG4*, SPG9B*, SPG11, SPG15, SPG21, SPG32, SPG35, SPG44, SPG45/SPG65, SPG47, SPG49, SPG50, SPG54, SPG55, SPG56, SPG63, SPG66, SPG67, SPG71, *KLC4*
Hydrocephalus (variable)	SPG1, SPG11*, SPG47, SPG50, SPG51
"Ears-of-the-lynx" sign	SPG11
Basal ganglia changes	SPG35, SPG43* (brain iron accumulation); SPG56 (calcification), *MT-CO3* (Leigh-like)
HSP with epilepsy	SPG2, SPG3A, SPG4, SPG6, SPG11, SPG15, SPG18, SPG35*, SPG44*, SPG47*, SPG49*, SPG50, SPG51*, CPSQ-I*
HSP with lower motor neuron disease (ALS-like phenotype)	SPG4*, SPG9A, SPG11, SPG14, SPG15, SPG17, SPG20, SPG21, SPG26, SPG38, SPG39, SPG43, SPG62, SPG64, *GRID2*
HSP with peripheral neuropathy	SPG2, SPG3A, SPG4*, SPG6, SPG7, SPG10, SPG11, SPG15, SPG17, SPG19*, SPG21, SPG23, SPG25, SPG26, SPG27, SPG30, SPG31, SPG36, SPG39*, SPG43, SPG55, SPG56, SPG57, SPG60, SPG61, SPG66, SPG68, SPG74, SPG75, SPOAN, *CCT5*, *FAM134B*, *LYST*, *MT-ATP6*
HSP with movement disorders	SPG9B, SPG10, SPG11, SPG15*, SPG20*, SPG21, SPG22, SPG26, SPG35, SPG44, SPG47*, SPG53, SPG56, SPG58, SPG67, SPOAN*, Spastic paraplegia with deafness*
HSP with cerebellar ataxia	SPG2*, SPG4, SPG5A*, SPG6*, SPG7, SPG9A*, SPG10, SPG15, SPG20, SPG21, SPG22, SPG26, SPG30, SPG31, SPG35, SPG44, SPG46, SPG49, SPG50, SPG58, SPG62, *EXOSC3*, *LYST*, *GRID2*, *MAG*, *TUBB4A*, *MT-TI*

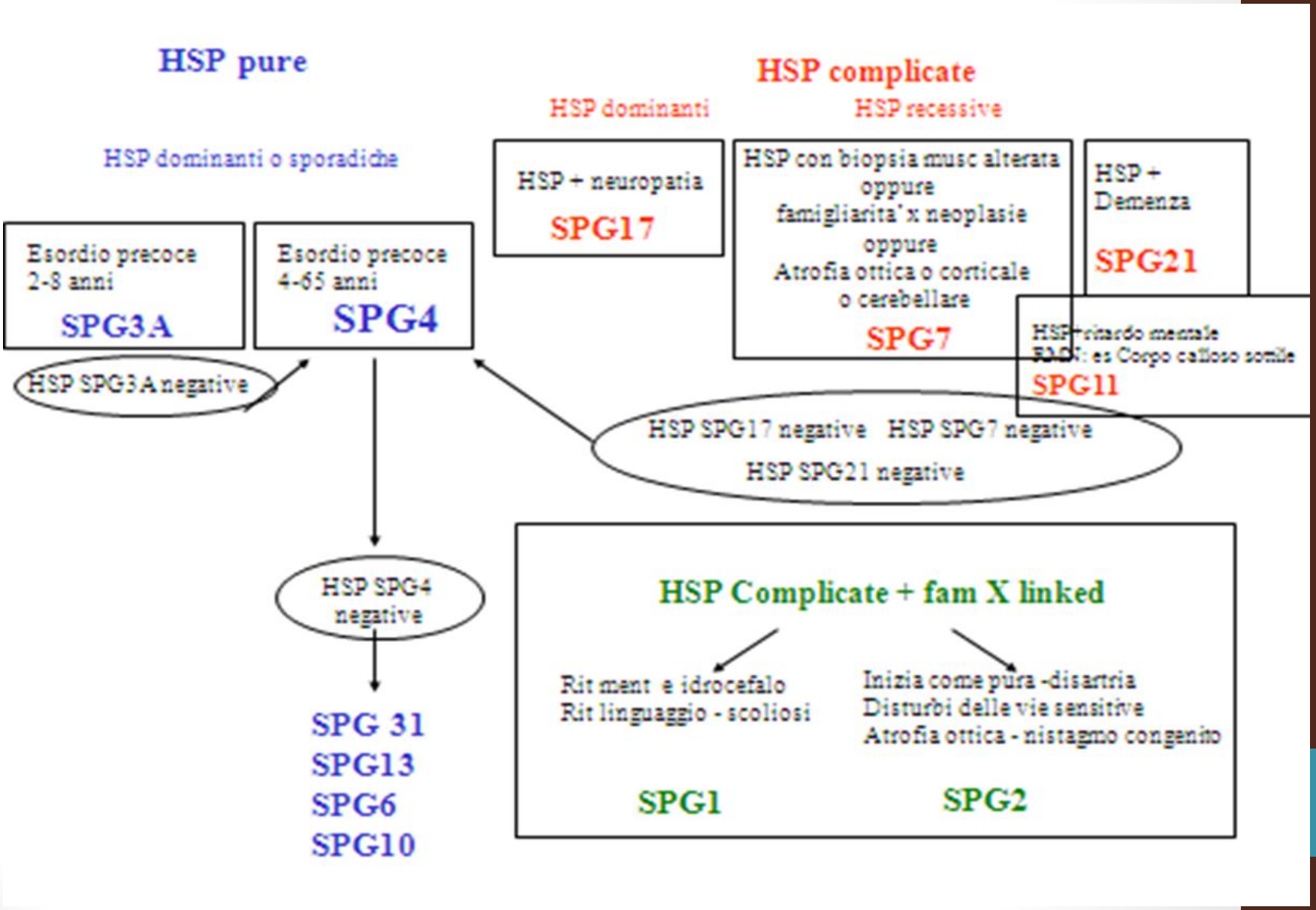
Table 4 (continued)

Clinical and neuroimaging parameters	Differential diagnosis of HSP
HSP with mental retardation (variable)	SPG1, SPG2, SPG3A, SPG4, SPG7, SPG9B, SPG10, SPG11, SPG14, SPG15, SPG16, SPG18, SPG20, SPG21, SPG22, SPG23, SPG26, SPG31, SPG32, SPG35, SPG44, SPG45/SPG65, SPG46, SPG47, SPG49, SPG50, SPG51, SPG52, SPG53, SPG54, SPG55, SPG56, SPG58, SPG59, SPG60*, SPG61, SPG62, SPG64, SPG66, SPG69, CPSQ-I, *EXOSC3*, *MAG*, *MT-CO3*, *MT-TI*
HSP with stereotypic laughter	SPG47, SPG51, SPG52*
HSP with optic atrophy (or other retinal changes)	SPG2, SPG3A*, SPG5A*, SPG7, SPG11, SPG15, SPG16*, SPG35, SPG43, SPG45/SPG65, SPG54, SPG55, SPG57, SPG68, SPG74, SPOAN, *MT-ND4*
HSP with opthalmoparesis	SPG7, SPG35*, *MT-CO3*, *MT-TI*
HSP with cataracts	SPG9A, SPG26, SPG46, SPG69, Spastic paraplegia with deafness
HSP with hearing loss	SPG15*, SPG29, SPG44, SPG46, SPG69, Spastic paraplegia with deafness, *MT-TI*
HSP with episodic central apnea	SPG49
HSP with upper gastrointestinal findings	SPG9A, SPG29, SPG49, SPG54
HSP with skin lesions	SPG23, SPG53*, *IFIH1*
HSP with dysmophisms (including microcephaly and macrocephaly)	SPG1, SPG9B, SPG16, SPG20, SPG22, SPG23, SPG47, SPG49, SPG50, SPG51, SPG52, SPG54, SPG55, SPG58, SPG64, CPSQ-I*
HSP with genetic anticipation	SPG29, SPG40

*Cases in which can rarely present as a to the pointed group

CPSQ-I cerebral palsy, spastic quadriplegic, type I; *SPOAN* Spastic paraplegia, optic atrophy, and neuropathy syndrome [1–3]

Algoritmo analisi genetiche «generale» (adulti/bambini)



Algoritmo analisi genetiche in caso di esordio età pediatrica

SPG3A(atlastina) : pura AD; Esordio prima dei 10 aa-mai dopo i 20 aa

SPG4 (spastina) : pura (quasi sempre) AD; Esordio sia infanzia che età adulta

SPG11 (spatacsina) ar, forma più frequente ad esordio infantile
SPG15 (ZFYVE26)ar, tra 5 e 19 aa

SPG7 (paraplegina) ar; Esordio tra 10 e 42 aa; più frequente adulti

SPG6 (NIPA1): pura AD; occasionale esordio infantile, più spesso adolescenza

SPG10 (KIF5A) ed SPG12
Pure, AD, esordio infantile

SPG17 (BSCL2) AD variabile età esordio, anche infanzia

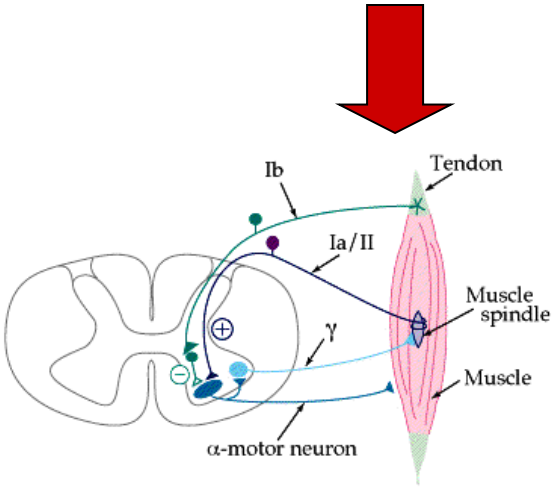
SPG31 (REEP1) pura AD
Esordio < 20 aa in 71% casi

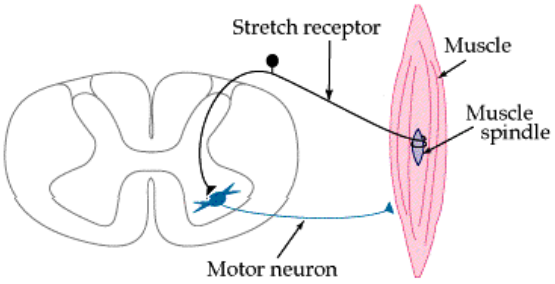
SPG1 (LICAM) ed SPG2 (PLP1)
X linked
Ritardo mentale

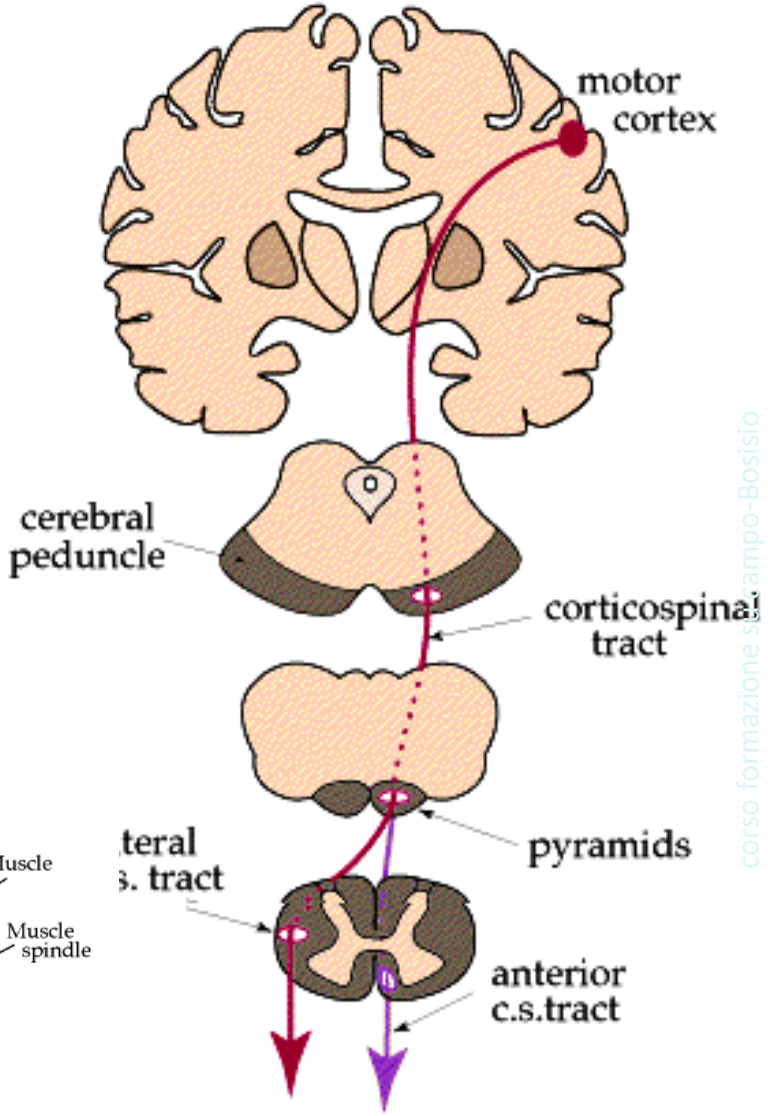
The principal neurological pathway over which signals pass to drive a deliberate movement can be divided into two stages.

1) In the first stage, a descending connection from neurones **("upper motor neurones")** in the motor cortex of the brain to cells in the anterior and posterior horns of the spinal cord

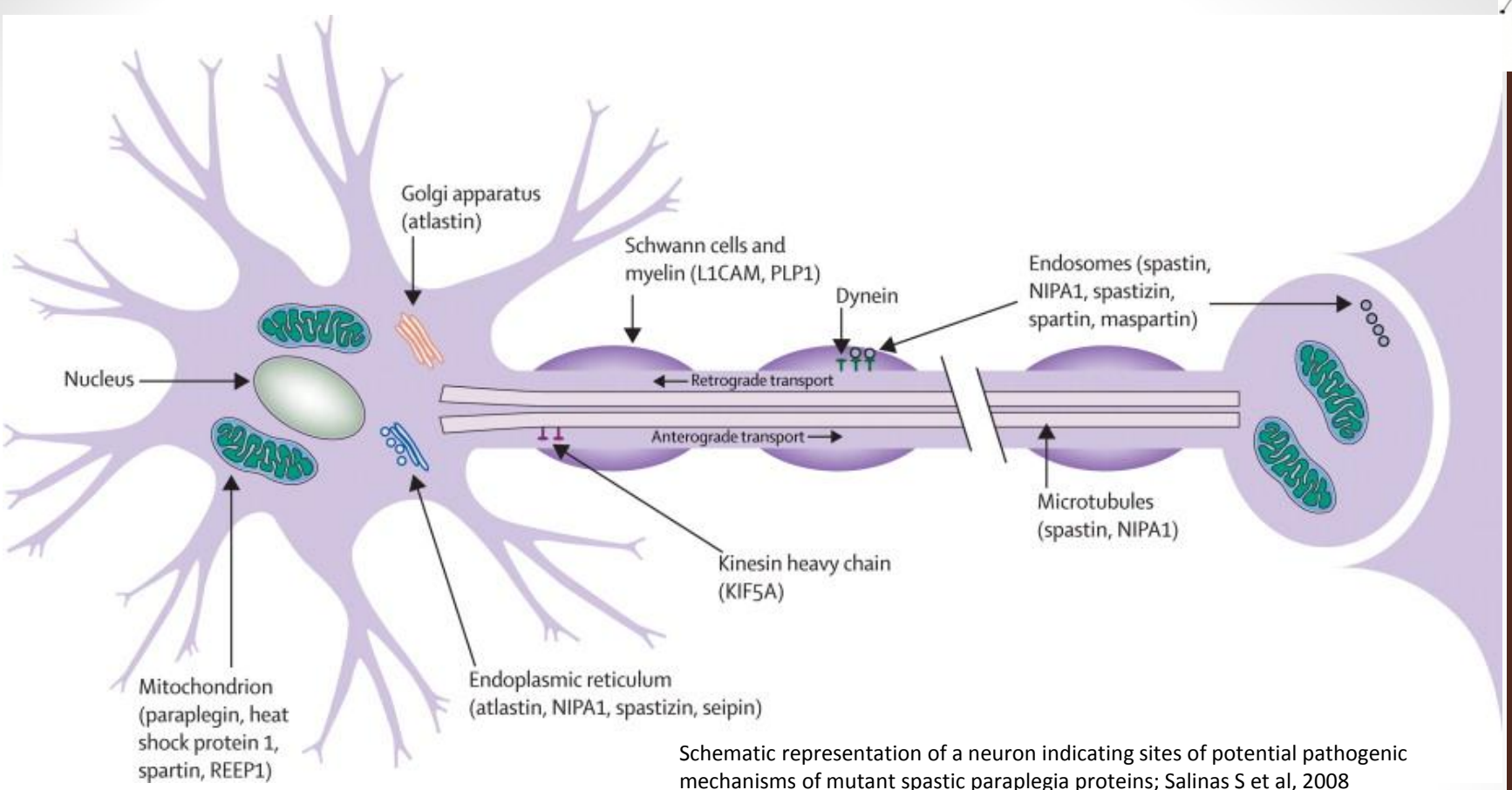
corticospinal tract







corso formazione sul campo-Bosisio P., aprile-giugno2012



Schematic representation of a neuron indicating sites of potential pathogenic mechanisms of mutant spastic paraplegia proteins; Salinas S et al, 2008

- Alterazione del trasporto assonale di macromolecole, organelli o altri trasportatori→ più evidenti in parti distale degli assoni(poss lunghezza anche di 1 metro)
- Alterazioni «traffico» a livello di membrana
- Alterazioni di funzionalità mitocondriale

HSP PURE

❑ SPASTIC PARAPLEGIA 4, SPG4;AD, PHSP CHSP

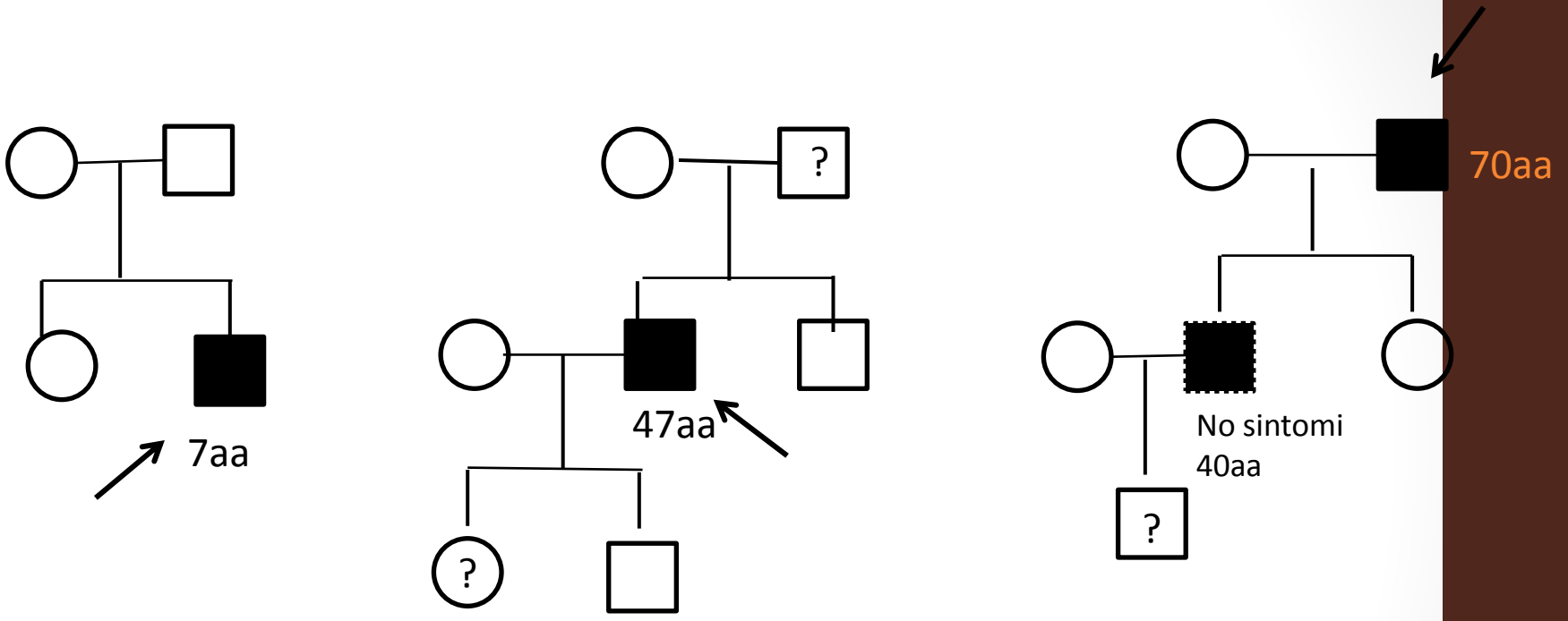
Gene map locus 2p22-p21 caused by mutation in the SPG4 gene that encodes the protein called spastin

30-45% of all pure ADHSP

Age of onset ranged from infancy to 63 years- Onset later than 35 ys→ faster progression than childhood onset

The clinical expression of the disorder within a family included:
✓ asymptomatic patients (25%)
✓ mildly affected individuals with spastic gait but able to walk independently
✓severely affected patients: wheelchair bound

-→ tutti Mutazione gene SPG4



❑ COGNITIVE DECLINE/IMPAIRMENT and SPG4

- ✓ Byrne et al. (1997, 1998) presented a family with autosomal dominant hereditary spastic paraplegia and a specific form of cognitive impairment → deficits in visual-spatial functions

Dysfunction manifested itself by difficulty in carrying out new tasks, forgetfulness, poor spatial perception, and impaired visual-motor coordination.

- ✓ McMonagle (2004) and Murphy (2009): active progression of cognitive deterioration and dementia in older patients with SPG4-ADHSP
- ✓ Tallaksen –Durr (2003): subclinical cognitive impairment primarly affecting executive functions more evident in SPG4 patients or carriers older than 50, more severe in the carriers of missense mutation than the those with truncating mutations
- ✓ Disturbances in executive functions in children→ not necessarely related to cerebral abnormalities

❑ Neuroimaging and SPG4

- ✓ Lesions in the cortical or subcortical structures (atrophy)→ resulting in dysexecutive syndrome (Tallaksen 2003)
- ✓ Dysplasia of the corpus callosum (Alber 2005)
- ✓ Congenital arachnoid cyst (Orlacchio 2004)
- ✓ Medullar atrophy
- ❖ Reduced cerebral blood flow (PET) in the left fronto-temporal cortex in 18 SPG4 pts with impaired cognitive functions (recognition memory of faces) [Scheuer , 2005)

❑ **Neuropathology**

Tangles in surviving neurons, tau-positive astrocytic inclusions, ubiquitin-positive intranuclear inclusions (particularly in pts with missense mutations in Spastin gene, White 2000)

- SPG3A (10% of AD pure HSP; most frequent in children)

FAMILIAL SPASTIC PARAPLEGIA 3,AD; PHSP

Gene map locus 14q11.2-q24.3, 14q11-q21

- caused by mutation in a GTPase gene that encodes the protein atlastin
- early-onset (between 1 and 7 yrs) and late onset

- progressive, usually severe, lower extremity spasticity
- Scoliosis (11%)
- Decreased vibration sense at ankles (27%)
- Sphinteric disturbances 17%
- Mean disease duration > 35 yrs
- Axonal neuropathy (rare, late development)

- In a family with 6 members affected with a very early onset severe form of spastic paraplegia, Dalpozzo (2003) identified a heterozygous mutation in the SPG3A gene.

All affected members had onset in infancy with delayed motor milestones, gait impairment, spastic paraparesis, distal atrophy, and lower limb weakness

- misdiagnosed with cerebral palsy (early onset)

atlastin

widely expressed, most abundant in brain and spinal cord

mutations in atlastin responsible for approximately 10% of autosomal dominant pure HSP

The dynamins, the group of proteins to which atlastin shows strongest homology involved in vesicle trafficking events, including recycling of synaptic vesicles and in the dispersion of mitochondria.

Association with microtubules ➡ action of neurotrophic factors and neurotrasmission

Caso clinico (da de Bot, 2010) SPG3A

Bimbo di 4 aa
Progressive difficoltà cammino ad esordio dei 12-13 mesi (inizio deambulazione)

Madre con minimi disturbi del cammino, ad esordio >35 aa
Nonna materna e zia materna disturbi analoghi ad esordio età adulta
Problemi non significativi da giungere ad attenzione medica

EON (bimbo)
Modesta spasticità del cammino
Aumento del ROT arti inferiori
Babinski presente bilat
Riduzione sensibilità pallestesica arti inf.

EON (madre e zia materna)
Minime anomalie della marcia
Segno di Babinski bilat

RMN encefalo e midollo nella norma
Esami metabolici nella norma

❑ SPG31 (3-6% of AD –pure HSP)

almost exclusively associated with a pure spastic paraplegia phenotype.

bladder disturbances and impaired vibration sense seems to be comparable to that reported in a large SPG4 sample (McDermott et al., 2006) and thus to be higher than in SPG3A (Durr et al., 2004).

peripheral neuropathy →rare in SPG31.

- ❖ SPG31 →fourth autosomal dominant form of HSP reported with age of onset predominantly in the first decade of life.
  However, adult onset patients are found and penetrance is incomplete

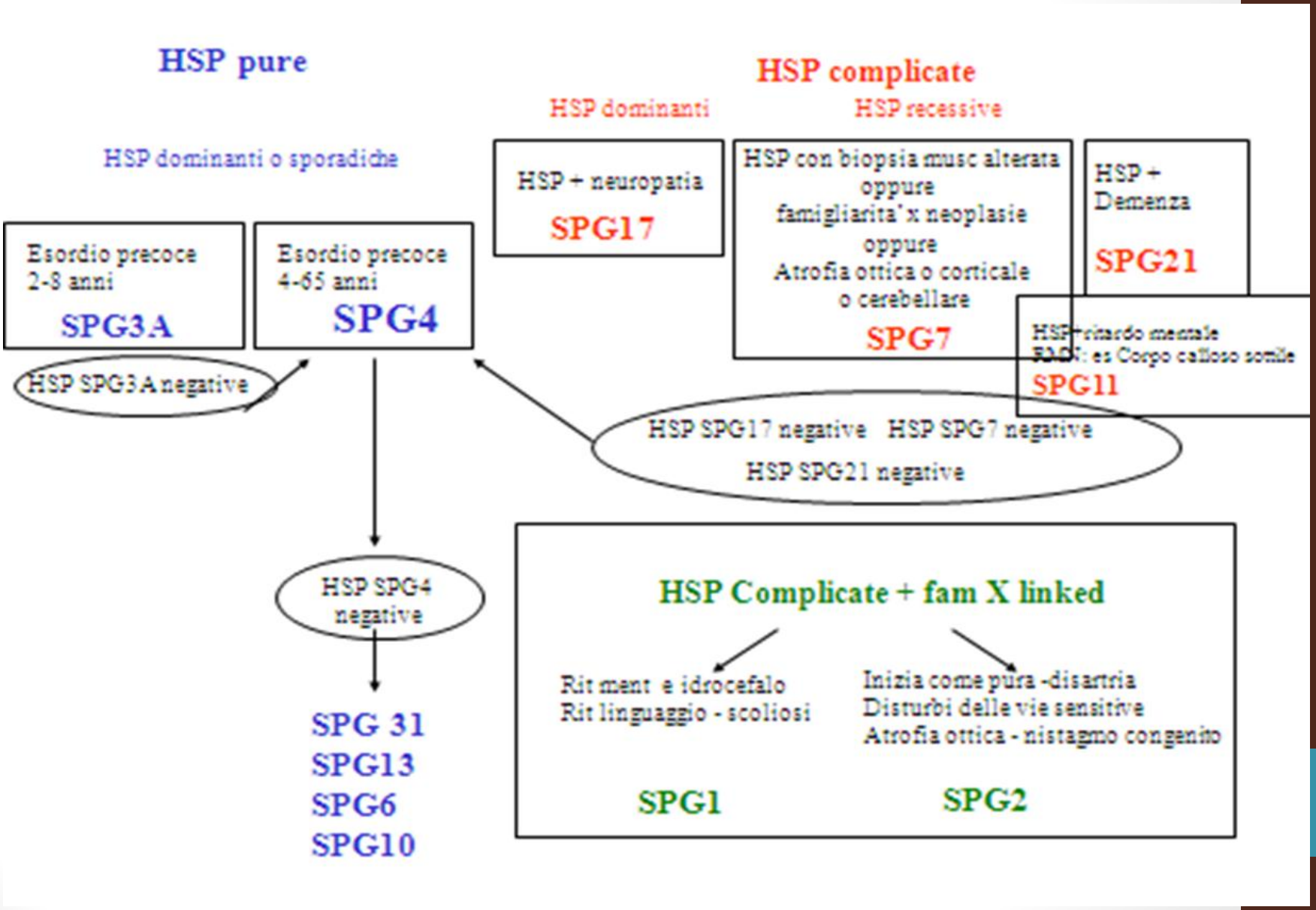
Mutations in the receptor expression enhancing protein 1 (REEP1)→
REEP1 expressed in various nonneuronal and neuronal tissues, including spinal cord→specific neurodegenerative phenotype despite the almost ubiquitous tissue expression

Mitochondrial expression/ Vesicle transport

Forme Complesse

- spasticità progressiva agli arti inferiori, ipostenia arti inf. disturbi dello sfintere urinario, modesta riduzione della sensibilità vibratoria e statochinestesica (di posizione) +
- Epilessia, ritardo cognitivo, demenza, amiotrofia, neuropatia periferica, coinvolgimento del sistema extrapiramidale e cerebellare, retinopatia, neuropatia ottica, sordità
- Molte forme di HSP complesse sono associate ad atrofia muscolare distale simmetrica di arti superiori ed inferiori

Algoritmo analisi genetiche «generale» (adulti/bambini)



Hereditary spastic paraplegia with thin corpus callosum (HSPTCC)

- → frequent subtype of complicated HSP and represents about 1/3 of the autosomal recessive forms of hereditary spastic parapaplegias

- HSP- TCC → clinically and genetically heterogeneous group.
- 7 distinct loci → SPG11,SPG 15, SPG 21, SPG 32, SPG 18, SPG 7 and most recently SPG 46 and SPG47.

- The major locus → SPG11 (OMIM 604360) which accounts for a variable percentage of families (41–77%) depending on the population examined [Crimella et al, J Med Genet 2009; Boukris et al, Neurogenetics 2010]

❑ Spastic Paraplegia type 7

Most affected individuals→proximal or generalized weakness in the legs and impaired vibration sense.

Onset →mostly in adulthood, although symptoms may start as early as age 11 years and as late as age 72 years.

- A pure phenotype of spastic paraplegia with hyperreflexia, extensor plantar responses, and mildly impaired vibration sensation in the distal legs
- In some individuals, a complicated phenotype of spastic paraplegia including pale optic disks, ptosis, slowed speech, swallowing difficulties, subtle cognitive impairment, upper motor neuron symptoms in the arms, urinary urgency, ataxia, nystagmus, strabismus, decreased hearing, scoliosis, *pes cavus*, motor and sensory neuropathy, and amyotrophy *[Harding 1983, De Michele et al 1998, Fink 2003, Wilkinson et al 2004, Elleuch et al 2006, Brugman et al 2008, Salinas et al 2008, Warnecke et al 2010]*

- Progression of disease may be rapid with severe disability after eight years' duration [*Elleuch et al 2006, Schüle et al 2006].*

- Prevalence: estimated at 2-6:100,000 for most countries.
- SPG7 → 5%-12% of autosomal recessive HSP *[McDermott et al 2001; Elleuch et al 2006, Brugman et al 2008; Salinas et al 2008; Casali, personal observation].*

Neuroimaging

- In a few individuals, conventional cerebral MRI may show cerebellar (or, less frequently, cortical) atrophy [*De Michele et al 1998*, *Wilkinson et al 2004*, *Elleuch et al 2006*, *Uttner et al 2007*, *Warnecke et al 2007*, *Salinas et al 2008*, *Hourani et al 2009*, *Warnecke et al 2010*].
- White matter changes as detected by diffusion tensor imaging (DTI) in the frontal lobes, the corticospinal tracts, and the brain stem →specific to SPG7-HSP (hereditary spastic paraplegia) [*Warnecke et al 2010*].
- subtle reduction of white matter integrity in the corpus callosum of heterozygote SPG7-autosomal recessive HSP carriers may be revealed by DTI, suggesting that different HSP-related genes share a common biologic pathway leading to neurodegeneration of the corpus callosum [*Warnecke et al 2010*].
- Spinal imaging studies → useful in the differential diagnosis, only????

- **Other investigations**

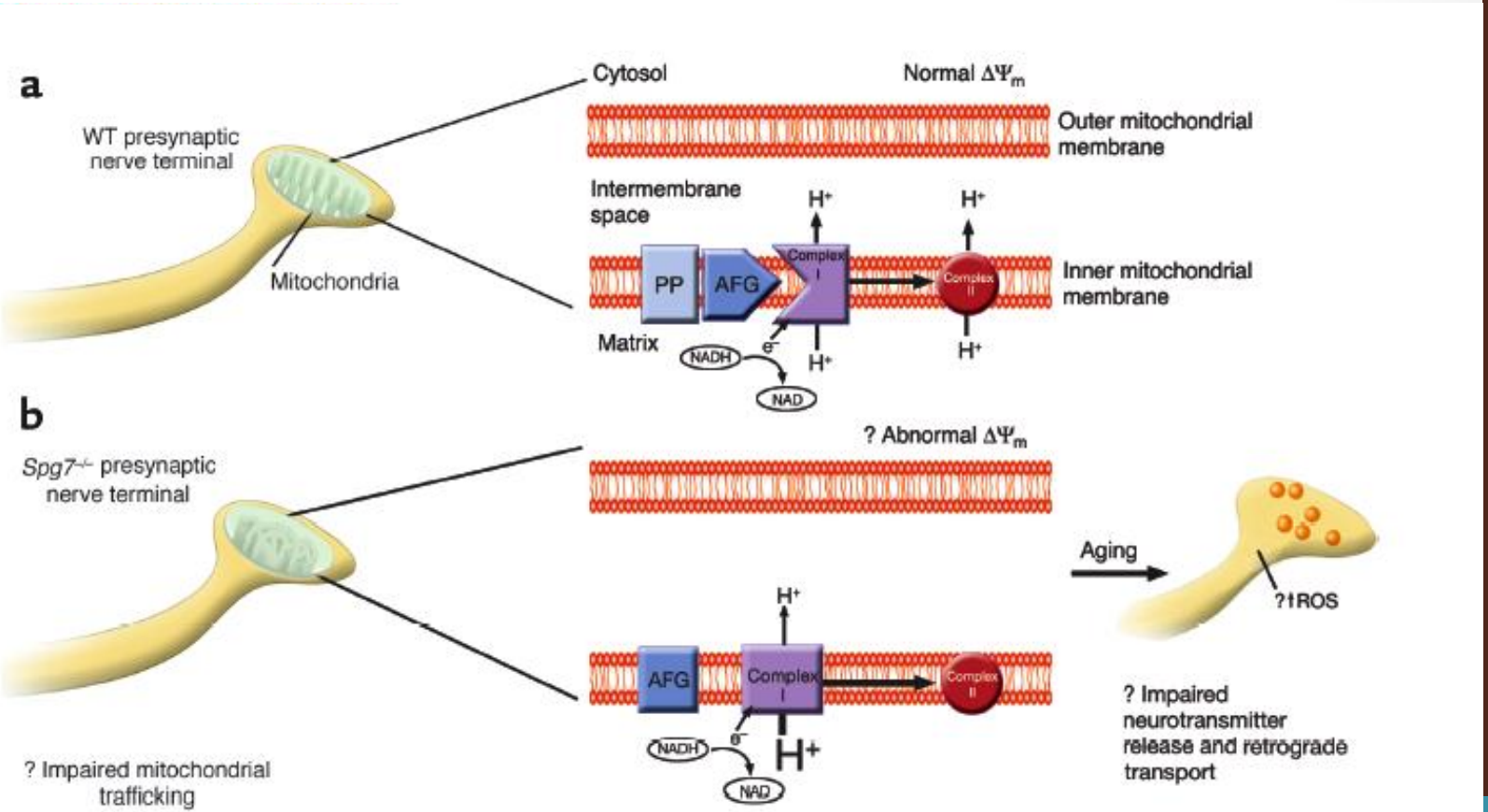
- **Spinal evoked potentials** → delayed prolongation of the central conduction time *[Nielsen et al 2001].*
- **Paired transcranial magnetic stimulation** (TMS) → delayed prolongation of the central motor conduction time and motor threshold in some **affected** individuals in lower limb muscles [*Warnecke et al 2007*, *Warnecke et al 2010*].
- **neuropsychological tests** → mild impairment of visuoconstructive and executive functions in some individuals [*Uttner et al 2007*, *Warnecke et al 2010*].
- CK: slightly increased
- Electromyography with nerve conduction velocities → axonal sensory motor neuropathy.
- Muscle biopsy → Changes of denervation with partial reinnervation
- Atrophic, angulated fibers, predominantly type II
- Ragged-red fibers, which are positive for the histoenzymatic reaction to succinate dehydrogenase (SDH) and negative for cytochrome *c* oxidase (COX, the complex IV of the mitochondrial respiratory chain), indicating an oxidative phosphorylation (OXPHOS) defect [*Casari et al 1998*, *McDermott et al 2001*, *Wilkinson et al 2004*, *Tzoulis et al 2008*].

- **Genetic counseling.** SPG7 is inherited in an autosomal recessive manner. Heterozygotes (carriers) are usually asymptomatic.
- Prenatal diagnosis

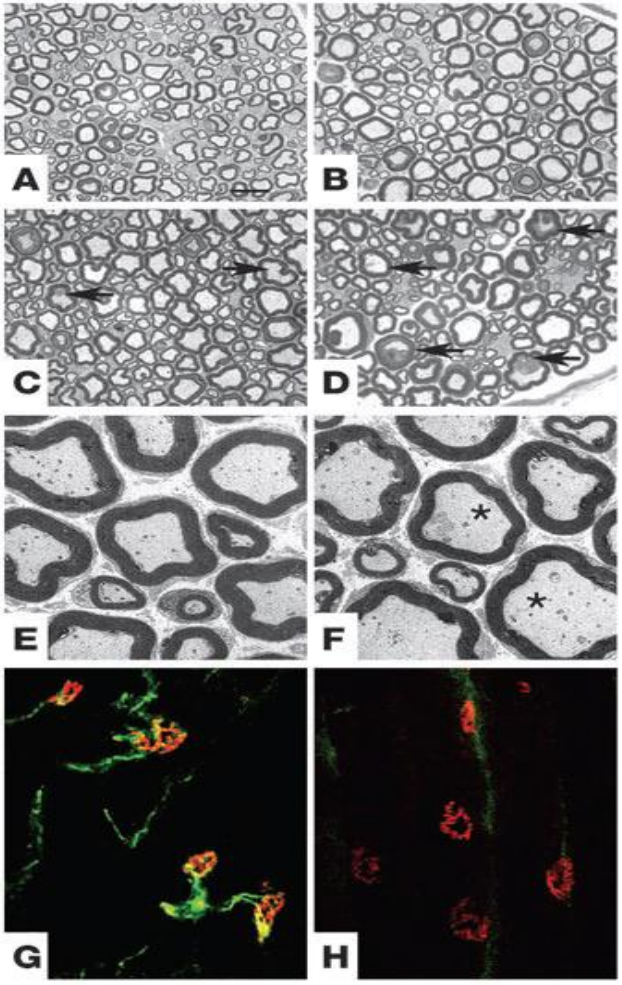
- *Treatment of manifestations:*
- Drugs that may reduce spasticity and muscle tightness include baclofen, tizanidine, dantrolene, and diazepam.
- Management of spasticity by intrathecal baclofen or intramuscular botulinum toxin injections may be an option in selected individuals [*Young 1994*].
- Physical therapy and assistive walking devices often reduce contractures, provide support, and promote stability.
- Occupational therapy helps with activities of daily living.

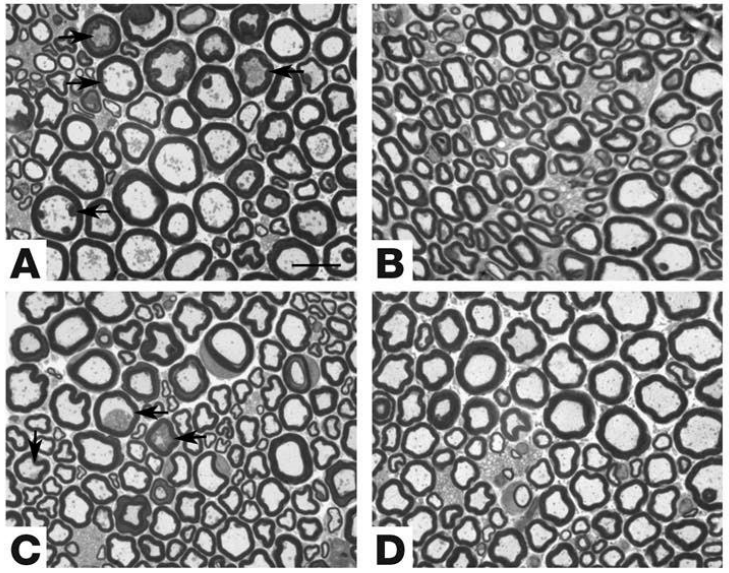
paraplegin → mitochondrial energy-dependent protease

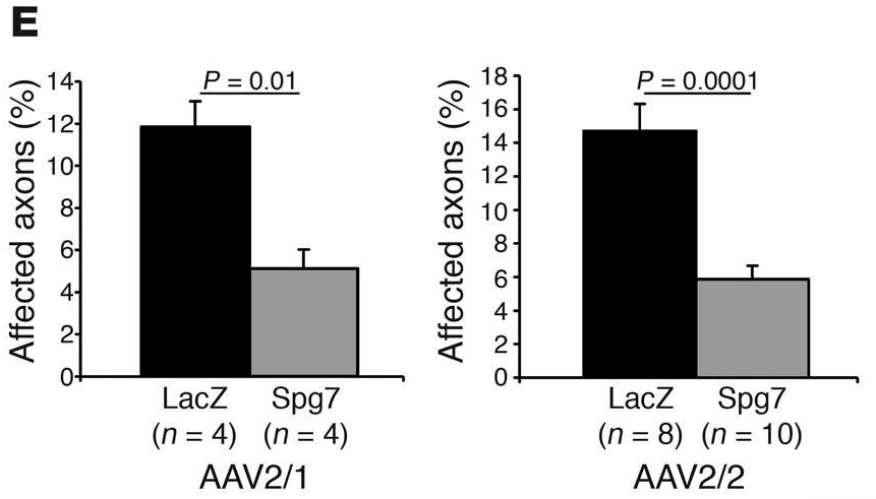
Paraplegin-deficient mice display a progressive degeneration in several axonal tracts--> characterized by the accumulation of morphological abnormal mitochondria



Adenoassociated virus–mediated (AAV-mediated) intramuscular delivery of paraplegin halted the progression of neuropathological changes and rescued mitochondrial morphology in the peripheral nerves of paraplegin-deficient mice



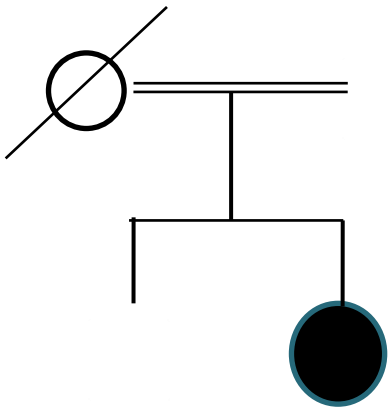




Marinella Pirozzi and Elena I. Rugarli
J. Clin. Invest. 116:202–208 (2006).

MP (male, 51 ys) MG (female , 46 ys)

@ The probands→ two siblings (brother and sister) born from consanguineous parents , with origins in the South of Italy.
@ Family history of thyroid disturbances and autoimmune diseases
@ Normal gestation and delivery and normal motor and language milestones.



- **Patient 1: male, 49 years old at time of last examination.**
- **Onset around the age of 40 years with mild dysartria and unsteadiness during walking.**
- **Over the next years a slowly progressive decline, with worsening of the gait disturbances with spastic paraparesis and dysartria.**
- **At time of first examination in our Department (age 47 years) → spastic paraplegia (increased tone, uncle clonus, brisk reflexes with Babinski sign) with unsteady but autonomous ambulation, dysartria, lateral beating nystagmus, and dysmetria.**
- **full IQ of 106, verbal IQ 114, performance IQ 94.**
- **Abormalities in acustic evoked potentials (delay in I-III)**

- **At the age of 49 years → still ambulant, with severe unsteadiness and frequent falls, dysartria and moderate cerebellar signs.**
- **Behavioural disturbances reported by the family members in the last years and a mild cognitive decline**
- **increased CK (2 - 4X the normal range); thyroid dysfunction, Hepatic steatosis**
- **Retinal detachment and early onset cataract are present.**
- **Abnormalities at motor evoked potentials and neurogenic signs at the electromyographic test**
- **muscle biopsy mild mitochondrial signs: COX negative fibers and few Ragged Red Fibers**

- **Brain MR scans (40 and 49 years of age)**

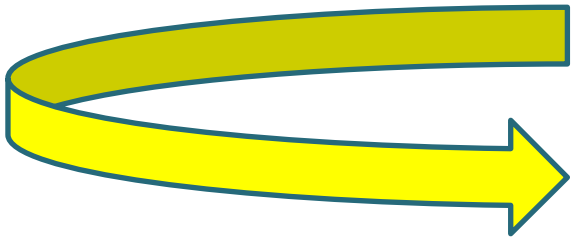
- **a progressive cerebellar atrophy associated with a markedly thinned corpus callosum.**
- **severe whole cerebellar atrophy associated with mild brainstem atrophy.**
- **brain emispheres atrophy**
- **marked hypo-intense signal on T2-weighted and FLAIR images at the level of red nuclei, bilateral substantia nigra and pallidi→ possible iron accumulation???**
- **White matter signal → normal.**
- **Spectroscopy → reduction of N-Acetyl-Aspartate peak in the cerebellum.**

Patient 2:female, 46 years old at time of last examination
Two pregnancies with cesarean delivery.
Thyroid dysfunction.

- Around the age of 38 years → stiffness of the lower limbs with unsteadiness during walking
- At 40 ys→ rapidly progressive urinary incontinence
- Clinical evaluation at the age of 41 → spastic paraplegia with severe pyramidal tract signs (prolonged clonus, bilateral Babinski) and very mild cerebellar signs. Brain imaging → mild cerebellar atrophy both in the vermis and in the emispheres and a thin corpus callosum. Spectroscopy : normal . EMG: Mild myogenic signs - muscle biopsy : mild mitochondrial signs.
- at the age of 43 → spastic paraplegia with moderate weakness of the tibialis anterior muscles and pes cavus, dysartria, nystagmus and dysmetria .
- IQ level (WAIS-R) was Full IQ 83, Verbal IQ 92 and Performance IQ 75.

- **At the age of 46→ the spastic paraplegia and the cerebellar signs were only moderately worsened since 3 years before, but she was presenting a mild cognitive decline.**

- MR exams performed at 43 and 46 years of age showed similar, but less severe brain findings than patient 1.
- The last examination acquired on a 3T system → moderate cerebellar and cerebral atrophy with thin corpus callosum. Red nuclei, substantia nigra and pallidi , slightly hypo-intense on T2 and FLAIR images.
- NAA peak in the cerebellum → reduced.



?

Patient 1 →
screened for mutations in *SPG11, SPG15*, *SPG7* and *SPG21* genes :
negative

Complete mutation analysis of *FA2H* → presence of a homozygous change c.509A>G (exon 4) leading to the p.Y170C substitution

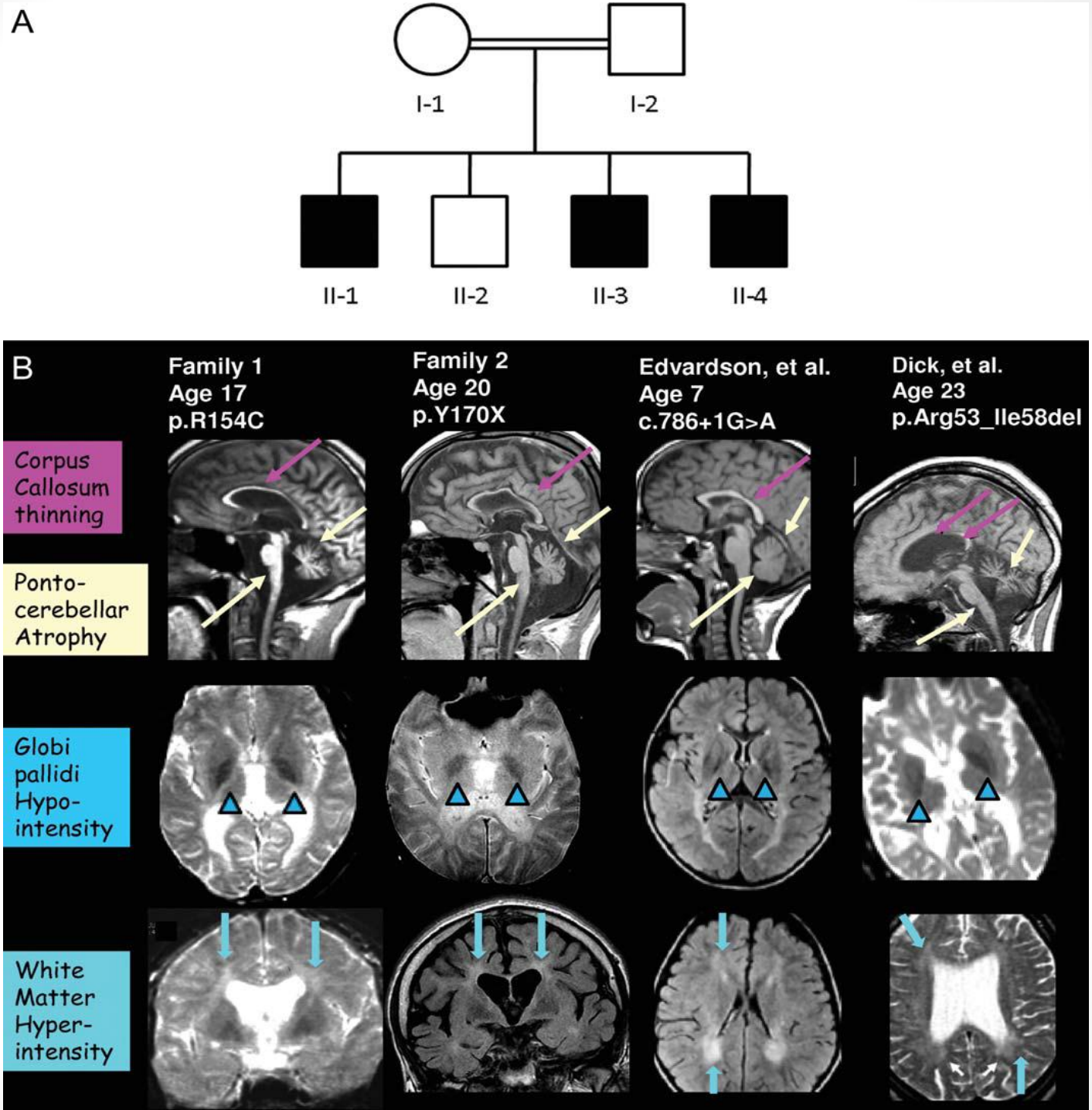
Present also in the sister

the **FA2H gene** encodes a fatty acid 2-hydroxylase catalysing the 2-hydroxylation of myelin galactolipids that account for one-third of the lipid content of the myelin sheath.

Homozygous FA2H mutations → associated with different neurodegenerative disorders such as

- ✓ leukodystrophy
- ✓ complicated form of spastic paraparesis with leukodystrophy (SPG35)
- ✓ form of neurodegeneration with brain iron accumulation (NBIA)
- ✓ and clinical pictures partly overlapping all three disorders.

ALL: fatty acid hydroxylase-associated neurodegeneration, FAHN → characterized by childhood onset of spasticity, dystonia, seizures, axonal neuropathy (in one family only), optic atrophy, cognitive decline, cerebellar atrophy, leukodystrophy and brain iron accumulation.


A
I-1
I-2
II-1
II-2
II-3
II-4
B
Family 1
Age 17
p.R154C
Family 2
Age 20
p.Y170X
Edvardson, et al.
Age 7
c.786+1G>A
Dick, et al.
Age 23
p.Arg53_Ile58del
Corpus Callosum thinning
Ponto-cerebellar Atrophy
Globi pallidi Hypo-intensity
White Matter Hyper-intensity

Publication	Edvardson et al.[3]		Dick et al.[4,8]		Kruer et al.[5]		Present article
Family	Family 1 and 2	Family 3	Pedigree 1	Pedigree 2	Family 1	Family 2	Present family
Mutation (DNA level)	c.786+1G>A	c.103G>T	c.703C>T	c.157_174del	c.460C>T	c.509_510delAC	c.270+3A>T
Mutation (protein level)	Skipping of exons 5 and 6	p.D35Y	p.R235C	p.R53_I58del	p.R154C	p.Y170X	Loss of exons 2–7
Age at onset	Childhood	Childhood	Childhood	Childhood	Childhood	Childhood	Childhood
Age at the time of publication (y)	20	12	25	31	>20	20	24
Spasticity	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dystonia	Severe	Absent	Mild	Severe	NR	Severe	Absent
Seizures	2/7	0/2	2/7	4/4	2/3	1/2	1/2
Ataxia	Mild	Absent	Absent	Absent	Mild	Mild	Mild
Cognitive decline	Mild	Absent	Mild	Mild	NR	Mild	Severe
Optic atrophy	Absent	Absent	Absent	Mild	Mild	Absent	Mild
Leukodystrophy (MRI)	Severe	Absent	Mild	Severe	Severe	Severe	Severe
Hypointensity of globus pallidus	Mild	NR	NR	Mild	Severe	Severe	Mild

1.Family/pedigree numbers are reported as indicated in the original articles. Every mutation was detected in a homozygous state. Age at the time of publication indicates the age of the older patient of that family described in the original article. NR, not reported; MRI, magnetic resonance imaging.

Terapie- Trattamento delle paraparesi spastiche ereditarie

→problema funzionale motorio essenziale: perdita di «equilibrio» con rischio di cadute

Fattori intrinseci alla base della manifestazione:

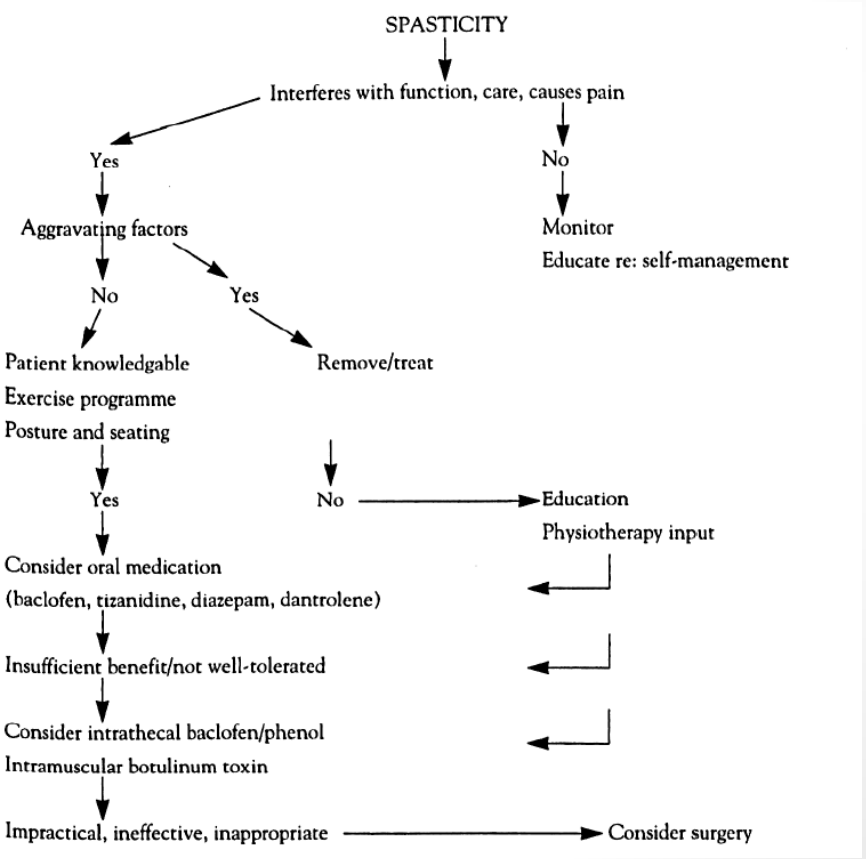
- SPASTICITA'
- RETRAZIONI MUSCOLOTENDINEE e DEFORMITA' ARTICOLARI
- IPOSTENIA MUSCOLARE
- DISTURBO PROPRIOCETTIVO

TERAPIE devono agire sui 4 FATTORI suddetti

SPASTICITÀ

- Trattamento chemodenervante locale con Tossina botulinica tipo A (BTX-A) im Clinicaltrials.gov: storia naturale-tossina botulinica
- Terapia per os: baclofene, eperisone e derivati- tizanidina
- Terapia con baclofene intratecale (ITB)
- Cannibis (Spray?? Tisana??)
- Neuromodulazione transcranica

(necessità di validazione)



RETRAZIONI MUSCOLOTENDINEE E DEFORMITA' ARTICOLARI

- Tossina botulinica tipo A
- Ortesi : tutori GP- serial Casting
- Chirurgia di allungamento muscolotendineo soprattutto distali agli arti inf

IPOSTENIA MUSCOLARE

- Attitudine a «non uso» di vari distretti muscolari
- Cammino
- Cycling: beneficio su tono muscolare, resistenza cardiorespiratoria, spasticità
- Idrochinesiterapia

DISTURBO PROPRIOCETTIVO

- Esercizi quotidiani per equilibrio (anche in autonomia al domicilio): ortostatismo alternato su 1 gamba con appoggio a tavolo alto ad esempio

- Robot assisted gait training: miglioramento pattern del cammino /pochi casi descritti

- C-Mill training: target visivo proiettato su tapis roulant

- Lokomat

- NeuroRehabilitation. 2015;36(1):93-9.

- **Robotic gait training improves motor skills and quality of life in hereditary spastic paraplegia. (**Bertolucci F et al)

- **METHODS:**
- **Thirteen** patients affected by uncomplicated HSP were subjected to a six-week robotic-aided gait training protocol. Participants underwent a battery of 3 walking test, 1 balance test and 2 quality of life questionnaires.
- **RESULTS:**
- At the end of the treatment a significant improvement of balance, walking ability and quality of life was observed in almost all the tests. The improvements were maintained over a two-month follow-up period.
- **CONCLUSIONS:**
- Our study indicates that a **robotic gait training** is **long term effective in improving balance and walking ability with a positive impact on quality of life** in patients affected by uncomplicated form of HSP. As currently there is no specific treatment to prevent or reverse HSP progression, our contribution would be significant for the development of exercise recommendations in this rare disease.

Grazie per l’attenzione