Staff du jeudi

23 octobre 2014

GHPS - Service de génétique

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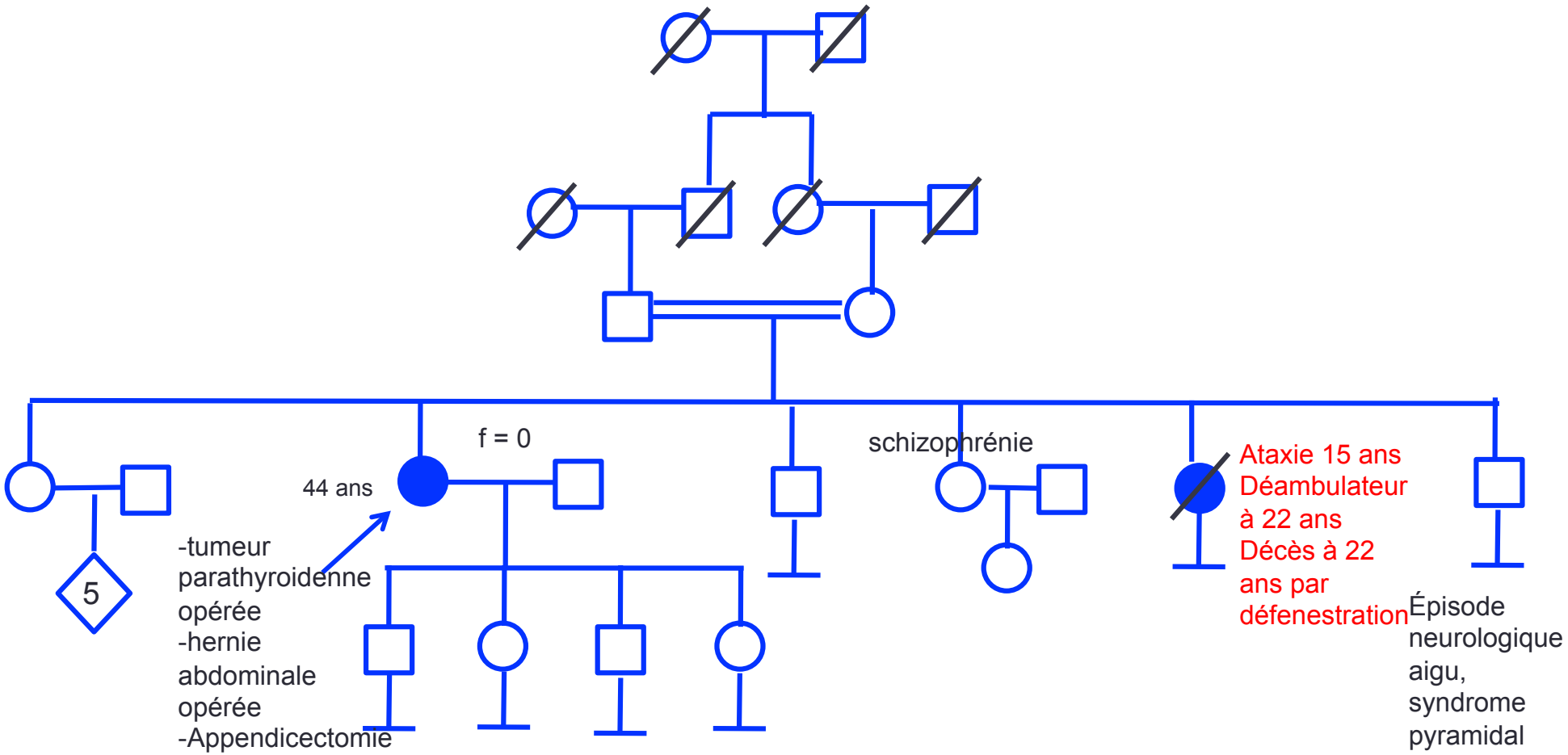
Origine Algérienne



- Troubles de la marche et de l’équilibre dans l’enfance.
- Aggravation progressive
- Chutes fréquentes. Marche avec une canne depuis l’âge de 39 ans.

44 ans

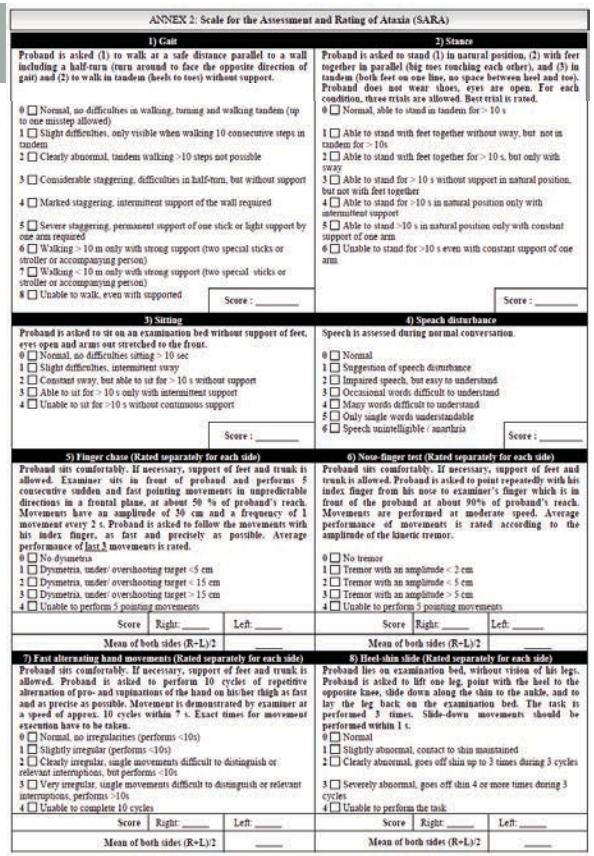
- Syndrome cérébelleux

Cinétique et statique, SARA 13/40

- Syndrome pyramidal avec BBK unilatéral
- Neuropathie clinique avec aréflexie,

apallesthésie, hypoesthésie, confirmée à l'EMG qui montre une neuropathie sensitive pure axonale

- Troubles oculomoteurs, ophtalmoplégie dans le regard vertical.



ANNEX 2: Scale for the Assessment and Rating of Ataxia (SARA)

1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

0 ☐ Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
1 ☐ Slight difficulties, only visible when walking 10 consecutive steps in tandem
2 ☐ Clearly abnormal, tandem walking >10 steps not possible
3 ☐ Considerable staggering, difficulties in half-turn, but without support
4 ☐ Marked staggering, intermittent support of the wall required
5 ☐ Severe staggering, permanent support of one stick or light support by one arm required
6 ☐ Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
7 ☐ Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
8 ☐ Unable to walk, even with supported

Score : _____

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other), and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

0 ☐ Normal, able to stand in tandem for > 10 s
1 ☐ Able to stand with feet together without sway, but not in tandem for > 10s
2 ☐ Able to stand with feet together for > 10 s, but only with sway
3 ☐ Able to stand for > 10 s without support in natural position, but not with feet together
4 ☐ Able to stand for >10 s in natural position only with intermittent support
5 ☐ Able to stand >10 s in natural position only with constant support of one arm
6 ☐ Unable to stand for >10 s even with constant support of one arm

Score : _____

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms out stretched to the front.

0 ☐ Normal, no difficulties sitting > 10 sec
1 ☐ Slight difficulties, intermittent sway
2 ☐ Constant sway, but able to sit for > 10 s without support
3 ☐ Able to sit for > 10 s only with intermittent support
4 ☐ Unable to sit for >10 s without continuous support

Score : _____

4) Speach disturbance

Speech is assessed during normal conversation.

0 ☐ Normal
1 ☐ Suggestion of speech disturbance
2 ☐ Impaired speech, but easy to understand
3 ☐ Occasional words difficult to understand
4 ☐ Many words difficult to understand
5 ☐ Only single words understandable
6 ☐ Speech unintelligible / anarthria

Score : _____

5) Finger chase (Rated separately for each side)

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband's reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

0 ☐ No dysmetria
1 ☐ Dysmetria, under/ overshooting target <5 cm
2 ☐ Dysmetria, under/ overshooting target < 15 cm
3 ☐ Dysmetria, under/ overshooting target > 15 cm
4 ☐ Unable to perform 5 pointing movements

Score	Right: _____	Left: _____
Mean of both sides (R+L)/2		_____

6) Nose-finger test (Rated separately for each side)

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90% of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

0 ☐ No tremor
1 ☐ Tremor with an amplitude < 2 cm
2 ☐ Tremor with an amplitude < 5 cm
3 ☐ Tremor with an amplitude > 5 cm
4 ☐ Unable to perform 5 pointing movements

Score	Right: _____	Left: _____
Mean of both sides (R+L)/2		_____

7) Fast alternating hand movements (Rated separately for each side)

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

0 ☐ Normal, no irregularities (performs <10s)
1 ☐ Slightly irregular (performs <10s)
2 ☐ Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s
3 ☐ Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
4 ☐ Unable to complete 10 cycles

Score	Right: _____	Left: _____
Mean of both sides (R+L)/2		_____

8) Heel-shin slide (Rated separately for each side)

Proband lies on examination bed, without vision of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and to lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s.

0 ☐ Normal
1 ☐ Slightly abnormal, contact to shin maintained
2 ☐ Clearly abnormal, goes off shin up to 3 times during 3 cycles
3 ☐ Severely abnormal, goes off shin 4 or more times during 3 cycles
4 ☐ Unable to perform the task

Score	Right: _____	Left: _____
Mean of both sides (R+L)/2		_____

- Mouvements oculaires montrant une hypermétrie des saccades en faveur d'un syndrome cérébelleux
- Lenteur de saccades avec nystagmus dissocié sur l'œil en adduction
- Pas de déficit moteur, pas d'amyotrophie, pas de diplopie, pas de signes urinaires

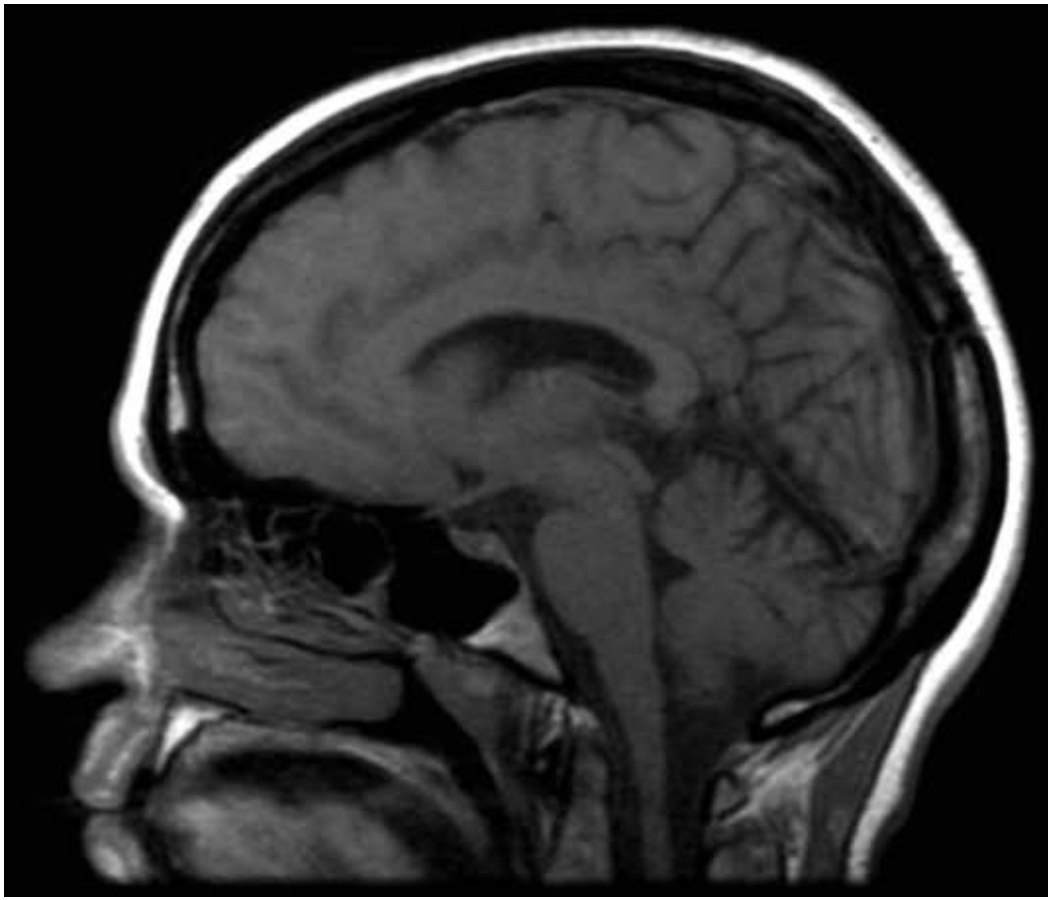
Résumé clinique

- patiente de 44 ans, origine maghrébine
- consanguinité, 2 cas dans la fratrie orientant vers une transmission récessive
- syndrome ataxo-pyramidal évoluant depuis l'enfance
- associée à une neuropathie sensitive pure axonale

HYPOTHESES DIAGNOSTIQUES ?

BILAN ?

Bilan d'un syndrome ataxo-pyramidal récessif avec neuropathie sensitive axonale pure



Pas d'atrophie cérébelleuse majeure

Bilan d'un syndrome ataxo-pyramidal récessif avec neuropathie sensitive axonale pure

- Pas d'expansion GAA dans FRDA
- Vitamine E < 1µM (N : 20-37)
- Mutation homozygote 744delA dans TTPA

➔ Diagnostic d'ataxie par déficit en vitamine E (AVED)

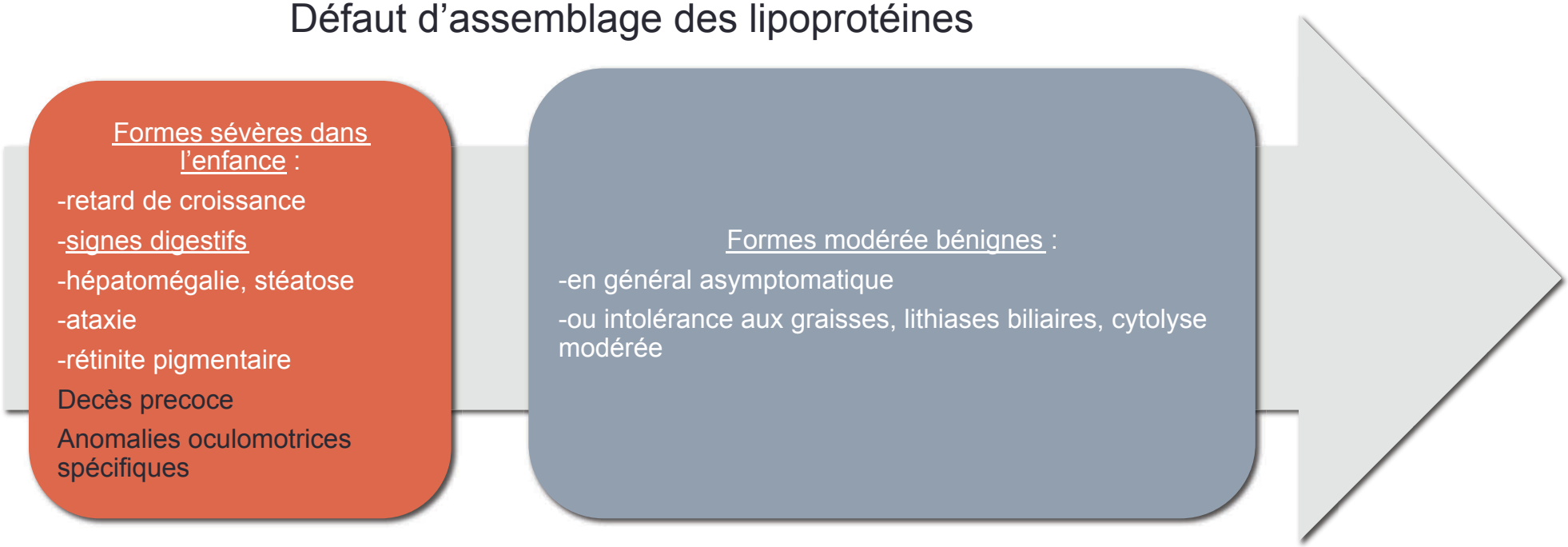
AVED / hypo et abetalipoproteinémie

- L'analyse des mouvements oculaires (ophtalmoplégie internucléaire et le déficit en vitamine E) peuvent faire évoquer une Abetalipoprotéinémie (Défaut d'assemblage des lipoprotéines) :
  - LDL cholestérol abaissé 0.85g/L (N 0.93-1.64)
  - apolipoprotéine B abaissée 0.67g/L (N 0.72-1.64)
  - Vitamine A abaissée 0.72µM (N 1.5-2.6)

MAIS … Tableau clinique incompatible

AVED / hypo et abetalipoproteinémie

Défaut d'assemblage des lipoprotéines



1/1 000 000,
mutations homozygotes gene MTTP ou gene APOB

1/1 000,
mutations hétérozygotes gène APOB ou gene PCSK9

LDL, triglycérides et apolipoprotéine B abaissés

(<5° percentile)

(5°-10° percentile)

Deficit en vitamine E, Clinique

- Début généralement avant 20 ans (2-52 ans),
- Ataxie progressive, en fauteuil vers l'age de 30 ans
- Tremblement du chef
- Neuropathie sensitive modérée
- Dystonie
- Syndrome pyramidal
- Parfois rétinite pigmentaire, diminution de l'acuité visuelle

Diagnostic

- Taux de vitamine E sérique < 2,5mg/mL
- Éliminer les causes de malabsorption
- Analyse moléculaire : TTPA, seul gène connu pour donner AVED, mutation retrouvée dans 90% des cas d'ataxies avec déficit en vit E
- Chez les hétérozygotes, taux sérique de vit E en moyenne 25% plus bas que la norme

Diagnostic différentiel AVED/Friedreich

AVED

- Rarement de cardiopathie, pas de tbles du rythme
- TREMBLEMENT DU CHEF
- PARFOIS RETINITE PIGMENTAIRE (H101Q)
- Neuropathie modérée

Friedreich

- CARDIOMYOPATHIE, troubles du rythme
- DIABÈTE
- Neuropathie sensitive pure sévère

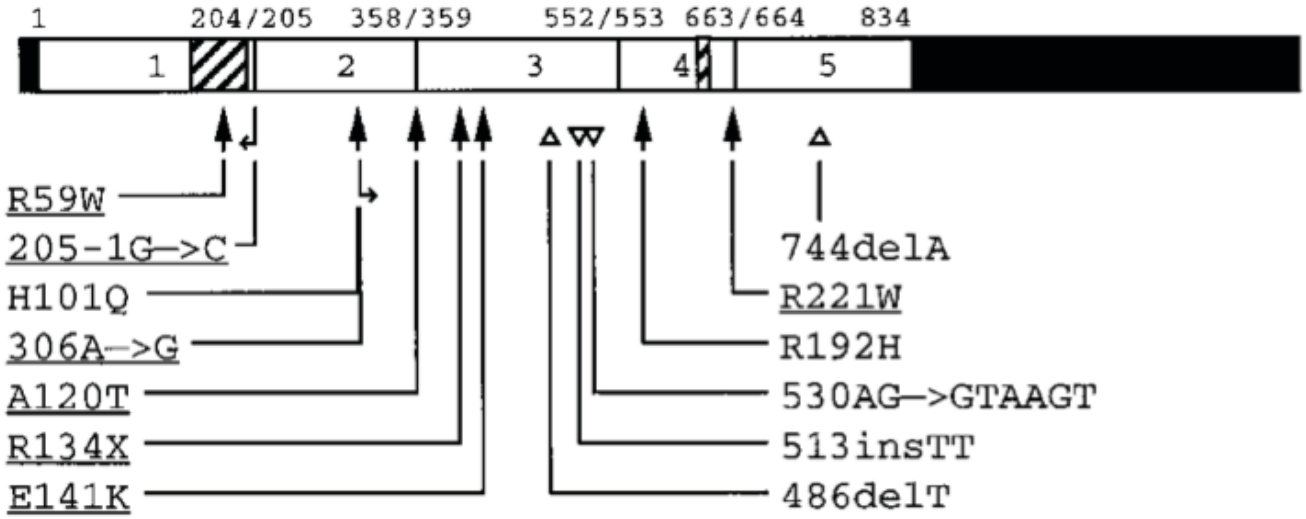
Avec amyotrophie, faiblesse musculaire, pieds creux

- Pas de rétinite pigmentaire

Epidémiologie

- Première description clinique en 1981
- Actuellement 220 patients rapportés, 106 familles dans le monde
- 23 mutations décrites
- Effet fondateur en Méditerranée (Tunisie++)
- 49 familles en Tunisie, dont 85% sont consanguines
- Mutation 744delA la plus fréquente (70%, Maghreb ++)
- Familles au Japon (mutation H101Q)

Genetique



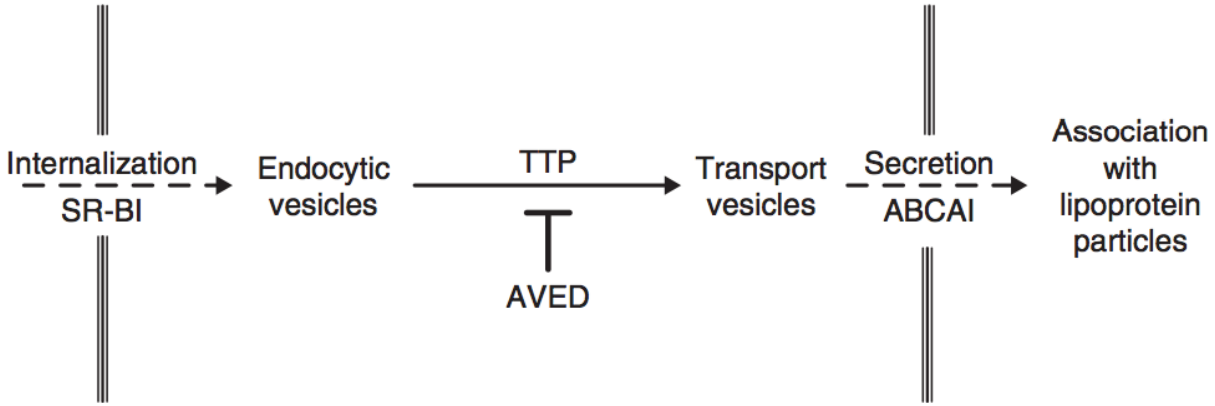
- Phénotype plus sévère avec mutation tronquantes
- Corrélations génotypes/phénotype :

  -mutation H101Q (japonaise) plus souvent associée à une rétinite pigmentaire

  -744delA (méditerranéenne) début précoce, sévère, risque augmenté de cardiopathie. Variation intra familiale.

Physiologie

- Molécule liposoluble antioxydante, d'origine végétale
- Pas de défaut d'absorption de la vitamine E (alpha-tocophérol)
- Mutation dans le gène de l'alpha-tocopherol transfer protein (*TTPA*) codant une protéine de transfert hépatique
- Défaut d'incorporation de l'isomère alpha tocophérol dans les VLDL
- Essentielle à l'intégrité des cellules de purkinje (modèle murin *Ttpa*$^{-/-}$)



Traitement

- 800 à 1500 mg de vitamine E par jour (TOCO500)
- Éviction du tabac (réduction du taux plasmatique de vitE)

Gabsi, 2001 – 24 patients

Table 4 Evolution of ARS scores and Vit E levels in AVED patients

	Serum Vit E levels ± SD	ARS values ± SD
Before treatment	0.55 ± 0.69	44.9 ± 18.39
After 3 months	7.39 ± 4.72	44.6 ± 18.66*
After 6 months	4.93 ± 3.62	41.23 ± 17.86*
After 9 months	8.07 ± 7.31	38.61 ± 4.33*
After 12 months	7.14 ± 6.46	35.7 ± 20*

*$P < 0.001$.

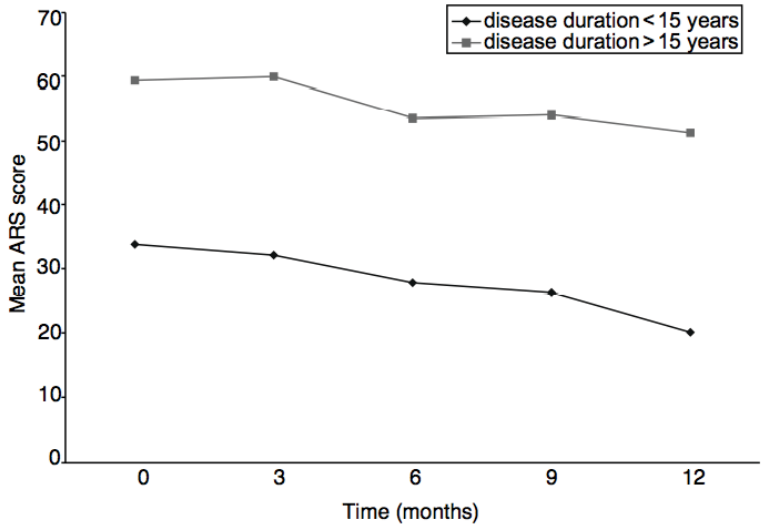


Figure 2 Evolution of ARS scores according to disease duration.

- Evolution variable sous traitement, stabilisation de l'état
- Efficacité d'autant meilleure que précoce
- Traitement pré symptomatique des enfants prévient l'apparition des troubles

Table 2 Principal clinical features of 16 AVED patients during vitamin E supplementation therapy

Patient	Vitamin E supplementation, mg/day	Duration of vitamin E therapy, years	Age at last examination, years	Serum vitamin E during therapy, mg/dl[a]	Gait at last examination[b]	Clinical observations during vitamin E supplementation
P0072	1200	11	50	1.40	3	Increased walking difficulty
P0071	1200	11	56	1.80	3	Stable neurological conditions
H0399	2000	10	32	1.08	3	Stable neurological conditions
P0597	1800–2400	6	47	0.91	4	Acute myocardial infarction at 46 years; increased dysarthria
P0048	1500	4	38	1.29	4	Stable neurological conditions
H0793	2100	13	26	1.10	1	Stable neurological conditions
P1368	100; 300; 900	10	32	0.80	3	Increased walking difficulty; irregular therapy intake
H0804	1000	5	39	NA	4	Diagnosis of RP at age 39 years
P0875	2400	5	19	0.92	1	Reduction of ataxia and dystonia
P0322	1200	6	32	1.12	1	Lower limb spasticity; increased head tremor
P0301	1200	6	35	0.84	1	Stable neurological conditions
P1060	2100	3	38	1.06	3	Increased walking difficulty
P0663	1200	2	48	1.99	2	Mild dysarthria
P1135	300	2	53	NA	3	Stable neurological conditions; irregular therapy intake
P1134	NA	2	52	NA	2	Stable neurological conditions; irregular therapy intake
P0570	1200	2	38	NA	4	Stable neurological conditions; sudden cardiac arrest at age 38 years

Stabilisation de l'état clinique dans 8/16, amélioration dans 1/16

Mariotti et al, 2004

Conseil génétique

- Autosomique récessif, risque de 25%
- Importance du traitement précoce des homozygotes présymptomatiques
- Pas de traitement des porteurs hétérozygotes (asymptomatique)

CONCLUSION

AVED

- Rarement de cardiopathie, pas de tbles du rythme
- Neuropathie modérée
- TREMBLEMENT DU CHEF

Friedreich

- CARDIOMYOPATHIE, troubles du rythme
- DIABÈTE
- Neuropathie sensitive pure sévère

Bibliographie

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Autres diagnostics éventuellement envisagés

- ataxie télangiectasie (αFP↗) mais phénotype moins sévère, pas de télangiectasies, pas d'immunodéficience, pas d'atrophie cérébelleuse
- AOA1 (albumine↘ cholestérol↗) mais pas d'apraxie oculomotrice, neuropathie moins sévère
- AOA2 (αFP↗ CPK↗) mais pas de polyneuropathie sensitivo-motrice
- ARSACS mais pas d'anomalies du TC, pas de polyneuropathie sensitivo-motrice
- Xanthomatose cérébro tendineuse (cholestanol↗) mais pas xanthomes, pas de signes psychiatriques

	AF	AOA1	AOA2	A-T
Age de début (ans)	16 (1-58)	7 (2-25)	15 (9-25)	< 5
Gène	*FRDA*	*APTX*	*SETX*	*ATM*
Fréquence relative	30-40%*	~5%	~8%	1-2%
Ataxie cérébelleuse	+	+	+	+
Neuropathie	S	SM	SM	SM
Signe de Babinski	+	0	(+)	0
Cardiomyopathie	+	0	0	0
Apraxie oculomotrice	0	+	+	+
Chorée	0	+	(+)	+
Télangiectasies, cancer	0	0	0	+
AFP	N	N	↑	↑
Albumine	N	↓	N	N
Cholestérol	N	↑	N ou ↑	N
Atrophie cérébelleuse	0	+	+	+

Ataxies récessives, avec signes cliniques particuliers et biomarqueurs

Ataxie avec déficit en vitamine E (debut 2-50 ans, moy 17)	Gène TTPA (alpha tocopherol transfer protein)	Maghreb Meme phénotype que AF + tremblement du chef	**Vit E** plasmatique effondrée	Supplémentation vitamine E et surtout prévention primaire (traitement précoce++)
Ataxie telangiectasie (début<5 ans)	Gène ATM Réparation ADN	telangiectasies, risque de cancer Infections récurrentes +- apraxie oculomotrice, mouvements involontaires, Neuropathie S-M axonale	↑ **alphaFP** **+- Déficit immunitaire (↓ IgA)**	Surveillance hématologique et tumeurs solides Attention RayonsX Veinoglobulines Hétérozygotes : ↑ risque cancer du sein
AOA1 (1-20 ans, moy 7)	Gène aprataxine	+/- apraxie oculomotrice et mouvements involontaires Neuropathie S-M axonale	↓**albumine** ↑**cholestérol**	Protocole en cours – coEnzyme Q10 (Pitié Salpetrière)
AOA2 (7-25 ans, moy 15)	Gène senataxine		↑ **alphaFP**	

Ataxies cérébelleuses récessives

Disease	Phenotype	Age at onset (yrs)	Diagnostic tests/ findings	Gene
Friedreich's ataxia	**Mixed cerebellar/sensory ataxia, areflexia, pyramidal weakness, extensor plantar responses**	**5-25 Late-onset possible**	**Mutation analysis**	**FRDA**
Hereditary ataxia with vitamin E deficiency	Like Friedreich, visual loss or retinitis pigmentosa, chorea.	<20	Low vitamin E Mutation analysis	TTPA
Infantile onset spinocerebellar ataxia	Hypotonia, neuropathy, areflexia, optic atrophy, ophthalmoplegia, hearing loss, involuntary movements, epilepsy	<2	Mutation analysis	C10orf2
Cayman ataxia	Hypotonia, psychomotor retardation	<20	Mutation analysis	ATCAY
Spinocerebellar ataxia with axonal neuropathy	Axonal sensorimotor neuropathy, distal amyotrophy, pes cavus. Mainly in Saudi Arabia.	<20	Raised cholesterol, Low albumin Mutation analysis	TDP1
Refsum's disease	**Polyneuropathy, sensorineural deafness, retinitis pigmentosa, anosmia**	**<20 Late-onset possible**	**Raised phytanic acid Mutation analysis**	**PHYH PEX7**
Abetalipoproteinaemia	Like Friedreich, retinitis pigmentosa, malabsorption	<20	Acanthocytes, hypocholesterolaemia Low vitamin E Mutation analysis	MTP
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	**Spasticity, severe neuropathy**	**<10 Late-onset possible**	**Mutation analysis**	**SACS**
Ataxia telangiectasia (AT)	**Oculomotor apraxia, conjunctival telangiectasias, extrapyramidal signs, predisposition to cancer**	**2-3 Late-onset possible**	**Raised serum α-fetoprotein Mutation analysis**	**ATM**
Ataxia telangiectasia-like disorder	Like AT, no telangiectasias	<20	Mutation analysis	MRE11

Disease	Phenotype	Age at onset (yrs)	Diagnostic tests/ findings	Gene
Ataxia with oculomotor apraxia type 1 (AOA1)	**Like AT, sensorimotor neuropathy, chorea, cognitive impairment**	**<20 Late-onset possible**	**Low albumin, high serum cholesterol Mutation analysis**	**APTX**
Ataxia with oculomotor apraxia type 2 (AOA2)	**Like AOA1, some features to a lesser degree**	**<20 Late-onset possible**	**Raised serum α-fetoprotein Mutation analysis**	**SETX**
Cerebrotendinous xanthomatosis	**Pyramidal or extrapyramidal signs, seizures, dementia, juvenile cataract, tendon xanthomas**	**<20 Late-onset possible**	**Bile alcohols in urine Increased levels of cholestanol Mutation analysis**	**CYP27**
Marinesco-Sjogren syndrome	Myopathy, cataract, skeletal abnormalities, hypogonadism, mild to moderate retardation	Infancy	High CK Mutation analysis	SIL1
Late-onset Tay-Sachs disease	**Areflexia, proximal muscle weakness and atrophy, behavioral problems**	**<20 Late-onset possible**	**Reduced activitiy of hexosaminidase A Mutation analysis**	**HEXA**
ARCA with psychomotor retardation	**Psychomotor retardation, disturbance of smooth-pursuit eye movement**	**50-56**	**Mutation analysis**	**SYT14**
SPARCA1	Cognitive impairment, esotropia, hypotonia	Early childhood	Mutation analysis	SPTBN2
ARCA2	Seizures, mental retardation.	1-11	Low levels of coenzyme Q10 in muscle biopsy	ADCK3/CABC1
SANDO/MIRAS	**Ophthalmoplegia, neuropathy, myclonus, dystonia, encephalopathy**	**15-40**	**Mutation analysis**	**POLG1**
Autosomal recessive cerebellar ataxia type 1 (ARCA1)	**Relatively pure cerebellar syndrome**	**17-50**	**Mutation analysis**	**SYNE1**
ARCA3	**Downbeat nystagmus, brisk reflexes**	**13-45**	**EMG: lower motor neuron involvement Mutation analysis**	**ANO10**
X-Linked Sideroblastic Anemia and Ataxia (XLSA/A)	Upper motor neuron signs in the legs of males, mild learning disabilities and depression, sideroblastic anemia	2-4	Whole blood count, mean corpuscular volume , peripheral blood smear Mutation analysis	ABCB7

Bilan d'un syndrome ataxo-pyramidal récessif avec neuropathie sensitive axonale pure

- IRM
- Ataxie de Friedreich
- Vitamine E (AVED)
- Albumine (AOA1)
- CPK (syndrome de Marinesco-Sjogren)
- Homocystéine
- αFP (ataxie télangiectasie, AOA2)
- Bilan lipidique (Abetalipoprotéinémie, AOA1 avec hypercholesterolémie LDL)

- Banque ADN