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X-LINKED ADRENOLEUKODYSTROPHY IN REPUBLIC OF MOLDOVA: CASE REPORT

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REZUMAT

Cuvinte cheie: X-ALD, VLCFA, maladie metabolică, insuficiență adrenocorticală.

Introducere: Adrenoleucodistrofia tip X-linkată (X-ADL) reprezintă o maladie metabolică peroxisomală cu afectare sistemică și evoluție progresivă. X-ADL este determinată de dereglarea beta-oxidării peroxisomale a acizlor grași cu catenă foarte lungă. Ca consecință, are loc acumularea VLCFA în plasmă și în toate țesuturile, inclusiv substanța albă a creierului, măduva osoasă și cortexul adrenal.

Materiale și metode: Se raportează cazul unui baiat de 13 ani diagnosticat cu X-ADL care manifesta cefalee, stângăcie, episoade de vome, hipoacuzie, ticuri ale ochiului drept, hiperpigmentarea pielii, crize hipotensive și mers ataxic progredient. S-a inițiat work-upul metabolic și RMN cerebral.

Rezultate: Investigațiile metabolice de prima linie nu au relevat modificări patologice semnificative. RMN cerebral (3T,0) a demonstrat schimbări demielinizante ale creierului foarte caracteristice pentru X-ADL. În urma evaluării concentrației VLCFA în sânge s-a determinat un nivel crescut al Acidului Cerotinic (C26:0) 2.30 μmol/L (*ref.val.<1.6*) și a ambelor rapoarte C24:0/C22:0 – 2.048 μmol/L (*ref.va.l<1.05*) și C26:0/C22:0 – 0.90 μmol/L (*ref.val.<0.029*), modificări specifice pentru stabilirea diagnosticului de X-ADL. În același timp, instalarea insuficienței adrenocorticală a fost relevată prin determinarea valorilor ridicate ale ACTH în sânge 109.7ng/dl (*ref. val.4.7-48.8*) și scăderea DHEAS 13,59 μg/dL (*ref. Val. 24-209*).

Discuții: X-ADL este una din cele mai progresive maladii peroxisomale cu un prognostic nefavorabil dacă nu este stabilit diagnosticul în stadiul preclinic. Expresia fenotipică a patologiei și pronosticul celor afectați este variabilă și impredictibilă. Forma cerebrală a X-ADL este una din cele mai severe fenotipuri. Creșterea concentrației VLCFA în sânge și modificările la RMN cerebral relevă elementele cheie în stabilirea diagnosticului de X-ADL. Transplantul de celule stem hematopoietice (HSTC) este raportată ca unica opțiune de tratament în perioada preclinică a patologiei. În cazul apariției modificărilor la RMN cerebral, inițierea HSTC nu este argumentată, iar eficiența procedurii este rezervată.

Concluzii: X-ADL reprezintă o patologie neurodegenerativă rapid progresivă asociată cu o morbiditate severă. Implementarea unor programe de screening neonatal pentru diagnosticul cât mai precoce al X-ADL, ar permite inițierea tratamentului în stare preclinică cu scăderea morbidității și mortalității infantile.

SUMMARY

X-LINKED ADRENOLEUKODYSTROPHY IN REPUBLIC OF MOLDOVA: CASE REPORT

Keywords: X-ALD, VLCFA, metabolic disease, adrenals insufficiency.

Introduction: X-Linked Adrenoleukodystrophy (X-ALD) is the most common metabolic peroxisomal disorder with systemic involvement and progressive evolution. VLCFA are accumulated in plasma and in all the tissues, including the white substance of the brain, in the spinal cord and adrenal cortex. It is caused by the mutation in ABCD1 gene localized on X chromosome.

Materials and methods: We report on a clinical case of a 10 years old boy hospitalized in the Institute of Mother and Child with X-ALD. Cerebral MRI and metabolic work-up investigations were used for diagnosis.

Results: The patient presents the following clinical manifestations: headaches during last 3 months, sometimes nausea, deafness, right eye tics, hyperpigmentation of the skin, progredient ataxic gait, hypotensive crisis "like lipothymia". MRI (3,0T) showed demyelinating changes of the brain very commune for X-ALD. The specific metabolic investigations for VLCFA showed a high level of Cerotinic acid (C26:0) 2.30 µmol/L (*ref.val.<1.6*) and both fractions C24:0/C22:0 – 2.048 µmol/L (*ref.va.l<1.05*) and C26:0/C22:0 – 0.90 µmol/L (*ref.val.<0.029*), the main parameters for X-ALD diagnosis. Endocrinological status showed a high level of blood ACTH 109.7 ng/l (*ref. val.4.7-48.8*) and low DHEAS 13,59 µg/dL (*ref. Val. 24-209*).

Discussions: X-ALD is one of the most progressive peroxisomal disorders with unfavorable prognosis if, the diagnosis is not established in the preclinical stage. The phenotypical expression and the prognosis of affected people is different and unforeseeable. The only option in the treatment of X-ALD cerebral form is the hematopoietic stem cell transplantation (HSCT), which is recomnded to be done only in the preclinical stage. In case of reported patient the HSCT it was not possible to perform because the clinical manifestations have already occurred.

Conclusion: X-ALD is a rapidly progressive neurodegenerative disorder that is associated with severe morbidity in the majority of affected patients. For an early diagnosis and a quickly intervention in treatment of X-ALD patients, it is necessary the implementation of program for neonatal screening of this pathology.

РЕЗЮМЕ

Х-СЦЕПЛЕННАЯ АДРЕНОЛЕЙКОДИСТРОФИЯ: КЛИНИЧЕСКИЙ СЛУЧАЙ

Ключевые слова: X-ALD, VLCFA, метаболическое заболевание, адренокортикальной недостаточности

Введение: Х- сцепленная адренолейкодистрофия (X-ALD) - это пероксисомалиная метаболическое заболевание с системным повреждением и прогрессирующим развитием. X-ALD вызывается нарушением пероксисомного бета-окисления жирных кислот с очень длинной цепью. В результате VLCFA накапливаются в плазме и во всех тканях, включая белое вещество головного мозга, костный мозг и кору надпочечников.

Материалы и методы. Сообщается о случае 13-летнего мальчика с диагнозом X-ALD, сообщающего о головной боли, неуклюжести, эпизодах рвоты, потере слуха, тиках в правом глазу, гиперпигментации кожи, приступах гипотонии и прогрессирующей атаксической походке. Было начато метаболическое обследование и МРТ головного мозга.

Результаты. Метаболические исследования первой линии не выявили значимых патологических изменений. МРТ головного мозга (3Т, 0) продемонстрировала демиелинизирующие изменения мозга, очень характерные для X-ALD. После оценки концентрации VLCFA в крови повышенный уровень церотиновой кислоты (C26: 0) был определен на уровне 2,30 мкмоль / л (справочная величина <1,6), и оба отношения C24: 0 / C22: 0 - 2048 мкмоль / л (справочный <1,05) и C26: 0 / C22: 0 - 0,90 мкмоль / л (справочное значение <0,029), специфические изменения для установления диагноза X-ALD. В то же время установка адренокортикальной недостаточности была выявлена путем определения высоких значений АКТГ в крови 109,7 нг / дл (ссылка Val 4.7-48.8) и снижения DHEAS на 13,59 мкг / дл (ссылка Val 24-209).

Обсуждение: X-ALD-одно из наиболее прогрессирующих пероксисомальных заболеваний с неблагоприятным прогнозом, если диагноз не установлен на доклинической стадии. Фенотипическое проявление патологии и прогноз больных изменчив и непредсказуем. Мозговая форма X-ALD-один из самых тяжелых фенотипов. Повышенные уровни VLCFA в крови и изменения на МРТ головного мозга выявляют ключевые элементы в постановке диагноза X-ALD. Трансплантация гемопоэтических стволовых клеток (HSTC) рассматривается как единственный вариант лечения в доклинический период патологии. В случае изменений на МРТ головного мозга начало HSTC не оправдано, а эффективность процедуры сохраняется.

Выводы: X-ALD-это быстро прогрессирующая нейродегенеративная патология, связанная с тяжелой заболеваемостью. Внедрение программ неонатального скрининга для как можно более ранней диагностики X-ALD позволит начать доклиническое лечение со снижением детской заболеваемости и смертности.

Introduction: X-Linked Adrenoleukodystrophy (X-ALD) is the most common metabolic peroxisomal disorder with systemic involvement and progressive evolution. X-ALD is determined by impaired peroxisomal beta-oxidation of very long-chain fatty acids (VLCFA), decreased with 30 % of the normal level [2,3]. Therefore, VLCFA are accumulated in plasma and in all the tissues, including the white substance of the brain, in the spinal cord and adrenal cortex [4]. It is caused by the mutation in ABCD1 gene localized on X chromosome [1]. The inheritance is X- linked in 95% of the cases and in 4,1% is a novo mutation. The X- ALD incidence is 1 per 17.000 new-born, it depend of the geographical situation [5].

Materials and methods. We report on a clinical case of a 10 years old boy hospitalized in the Institute of Mother and Child with X-ALD. Cerebral MRI and metabolic work-up investigations were used for diagnosis.

Results. The patient is the second child in a nonconsanguinous couple. The elder brother is healthy. Eredocolateral history: an uncle – a mother`s brother died at 7 years old from unknown reason, having speaking problems. The patient presents the following clinical manifestations: headaches during last 3 months, sometimes nausea, deafness, right eye tics, hyperpigmentation of the skin, progredient ataxic gait, hypotensive crisis "like lipothymia". At the beginning the child was consulted by a neurosurgeon being suspected a volume intracerebral process which was excluded by the cerebral MRI (1,5T) with leukodystrophy suggestions. There a metabolic work-up has been done which included: amino acids in blood and urine with nonsuggestive modifications for amminoacidopathies (Institute of Physiology and Sancreatology of Academy of Science, Chisinau, Republic of Moldova), with normal lactate status, acylcarnitinic profile (Cytogenomic Lab, Bucharest, Romania). The biochemistry was without significant changes and anion gap 16,5 mmol/L (n=7-16). Repeated MRI (3,0T) showed demyelinating changes of the brain very commune for X-ALD, dilatation of Galen vena, supracerebral arachnoid chyst 24*17 mm and otomastoiditis (fig. 1). The audiometry showed mild deafness transmission type like "word deafness", representing the difficulty perception of spoken language. The specific metabolic investigations as VLCFA has been done in Germany. The blood test for VLCFA done in the Metabolic Center from Heidelberg, Germany showed a high level of Cerotinic acid (C26:0) 2.30 μmol/L (*ref. val.<1.6*) and both fractions C24:0/C22:0 – 2.048 μmol/L (*ref.va.l<1.05*) and C26:0/C22:0 – 0.90 μmol/L (*ref. val.<0.029*), the main parameters for X-ALD diagnosis. Considering the adrenocortical insufficiency (hypotensive crisis, hyperpigmentation of the skin) was examined by endocrinologist and there were made tests that showed a high level of blood ACTH 109.7 ng/l (*ref. val.4.7-48.8*) and low DHEAS 13,59 μg/dL (*ref. Val. 24-209*). With the purpose of excluding X-ALD to the elder brother were evaluated VLCFA, they were in normal value (table 1). We initiated a symptomatic treatment with Hydrocortizol and Lorenzo oil. At the moment, the patient is 13 years old, the disease is progressing and during the year the general state became worse, he lost hearing, eyesight, speaking, locomotion and sitting abilities. As the demyelinating areas expended, appeared trigeminal pain resistant to opioid namely to Promedolum. Now, the child is in pre-coma, takes a symptomatic treatment, eats through the nasogastric tube and benefits of palliative care.

Table1.

Values VLCFA of the pacient and healthy elder brother

VLCFA	Normal values nmol/L	Pacient	Healthy elder brother
C24:0/C22:0	0.55-1.05	**2.048**	0.9
C26:0/C22:0	0.005-0.029	**0.90**	0.012
C26:0	0.2-1.6	**2,30**	0.45

Discusion: X-ALD is one of the most progressive peroxisomal disorders with unfavorable prognosis if, the diagnosis is not established in the preclinical stage. Clinical is characterized by some phenotype (tab. 2):

- **Addison phenotype** characterized by adrenal cortex insufficiency manifested at boys between 2 years old and teens period, more frequent at the age of 7,5. X-ALD is the reason of Addison disorder at boys and men. [6,7] that's why it is important to analyze X-ALD to each male that has Addison disorder. In early stages it affects the adrenals glucocorticoids function and then mineralocorticoids function [6].
- **Cerebral phenotype** (CALD) it is the most sever phenotype with progressive evolution, manifested between 4 and 8 years old. Initially appear clinical manifestation like deficit of attention, hyperactivity, after following the affection of cognition, blindness, auditory impairment ("word deafness" reflecting impairment in acoustic analysis of sounds), affection of motility, requiring full-time nursing and the total decline in 1-2 years. CALD can appear in the teens and adults period, but it is less possible.

Table 2.

X-ALD phenotypes and their frequency.

Phenotype	CALD childhood period	CALD teen period	CALD adult period	phenotype AMN		phenotype Addison
				without cerebral affection	with cerebral affection	
Frequency (%)	31-35	4-7	2-5	40-46	20	diminution with the age
Debut period (age)	2,5-10	10-21	>21	>18	>18	>2
Progression	fast	fast	fast	slow	fast	-

- **Adrenomieloneuropathy** (AMN) appears after 20 years old with progressive paraparesis, sphincters and sexual dysfunction, affection of adrenocortical function. All symptoms are progressive during the one decade.

About 20 % of women carrying mutation in ABCD1 gene present the same clinical neurological manifestation as the adrenomieloneuropathy phenotype, but after 35 years old in a milder form as the men [8]. The phenotypically expression and the prognosis of affected people is different and unforeseeable. Cerebral X-ALD form is one of the most sever phenotype. A new-born male has the risk in 35- 40 % cases to develop the disease if the mutation of ABCD1 gene occurs. There is a correlation between the debut of cerebral form and the pathology prognosis: as the debut of the early cerebral demyelination, the disorder progresses. The patients are neurological unaffected until cerebral MRI modifications don't appear.

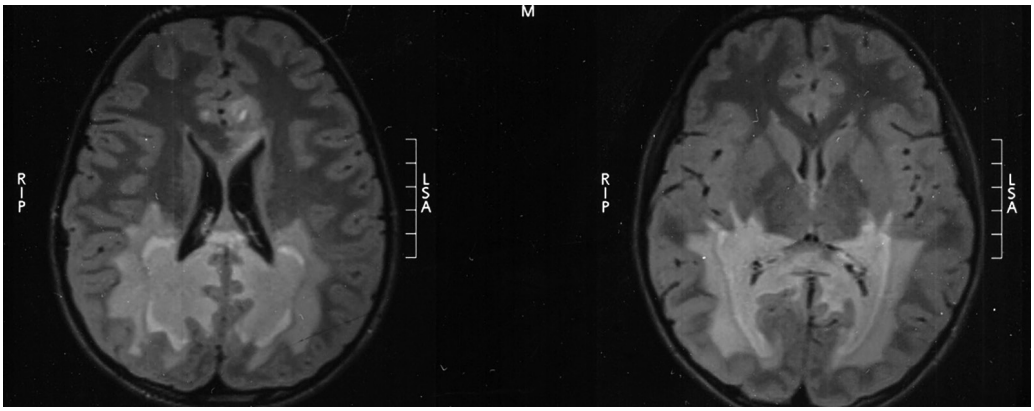

Fig.1 ***In the presented clinical case of the patient cerebral modifications of cerebral MRI were characteristic for X-ALD***

The patient benefited of complex diagnosis tests that helped to confirm the diagnosis and the consequences appeared during the evolution of the disorder. The state of the patient was evaluated by a large clinical evaluation and metabolic work-up. To confirm the diagnosis there were used modern methods like: cerebral MRI (3,0T) and determination of a high concentration of VLCFA in plasma through ionized Mass-spectrometry electrospray (ESI-MS) in neuropediatric section of "Medical clinic for children and teens from Gottingen", Germany. A team that includes a geneticist, pediatrician, neurologist, endocrinologist, cardiologist and rehabilitologist that supports the family and supervises the patient. There was initiated a treatment with Hydrocortisone 15mg/ per day, Diazepam rectal tub, Novalgin 100mg, Lorenzo oil, Promedol, fenobarbital, but without any results. The only option in the treatment of X-ALD cerebral form is the hematopoietic stem cell transplantation (HSCT). The result of this procedure is poor (with 5 years in 60 % with considerable neurological manifestations), but 5 years survive 90 % only if is made at early stages of cerebral form with minor lesions showed by MRI and a good clinical condition (there are not severe hotbeds and an IQ 80) [13,15,16]. In some publications is mentioned about 5-10 % of mortality after the HSCT and it depends on different factors [13]. In preliminary researches from Germany and France, the HSCT is more effective for adults with cerebral form than for the children with the same form because the post-transplant death is higher [17]. The transplant done in the childhood prevents the debut of the peripheral myelopathy and neuropathy in the adult period because HSCT removes the inflammatory component of the X-ALD cerebral form but not changes the biochemical effects that are toxic for the target tissues[18]. In the case of the reported patient there was used the Lorenzo oil considered one of the option of dietetic treatment. The Lorenzo oil was taken orally and had as components oleic acid (C18:1) and erucic (C22:1) both with triglyceride and have normalize the concentration of C26:0 during a month of a majority patients diagnosed with X-ALD [19, 20]. Unfortunately, usually this treatment does not reduce the C 26:0 level in the central nervous system, but only in plasma [21]. Other option of treatment can be Lovastatina, in the case of our patient was not possible to be administrated. This substance reduces VLCFA, but a clinical research showed that it has no influence on the C26:0 fraction [28]. Experimental evidence suggests that the debut of neurological manifestations of mutations in ABCD1/ABCD2 can be preventing by an antioxidant cocktail (N-acetyl-cysteine, α-lipoid and E vitamin) [22]. At the moment, a clinical research in Spain with a mixture made of N-acetyl-cysteine, a-lipoid and E vitamin has been started [23].

The families that have at least one boy with X-ALD diagnosis, men with X-ALD and carrying women needs a genetic consultation for finding the carrying people who can benefit of a prenatal diagnosis, asymptomatic and presymptomatic therapeutically intervention. Regular follow-up of presymptomatic boys can prevent death and morbidity. Prenatal diagnosis can be made at 11- 12 weeks of pregnancy from chorionic villus or at 15- 18 weeks of gestation from amniotic cells. In some countries, it is

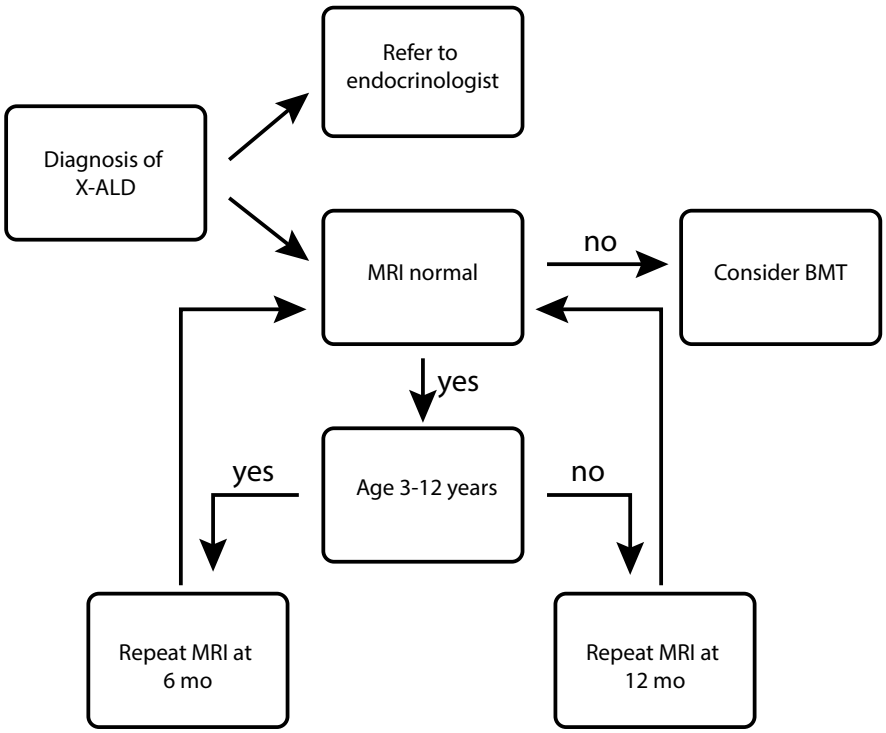

Fig 2. ***The surveillance algorithm of X-ALD***

possible the prenatal preimplantation diagnosis. If the fetus is a female, the prenatal diagnosis is not necessary because of variable expression of the disorder at women. In February 2016, X-ALD was recorded in the uniform Panel of screening recommended by USA that is the list of all genetic disorders recommended for the program of neonatal screening [24, 25]. The early diagnosis of X-ALD for boys is important for two reasons: the diagnosis of the adrenal insufficiency for initiate a substitution therapy with mineralocorticoids and the precocious diagnosis of the X-ALD cerebral form for a HSCT. Patients diagnosed with X-ALD need a permanent medical supervision. There is recommended to supervise the boys and the men diagnosed with X-ALD according the algorithm (fig.2). Due to the presence of the adrenal insufficiency in X-ALD, it is recommend to make a differential diagnosis with Addison disorder. The endocrinologists should perform the accumulation tests of VLCFA to boys and men whose test of antibodies of adrenal cortex are negative or when there are present the myelopathy signs. The confirmation of the diagnosis in our case was limited by the absence of diagnosis tests in our institute and the necessity of making the investigations in other medical clinics abroad.

Conclusion. X-ALD is a rapidly progressive neurodegenerative disorder that is associated with severe morbidity in the majority of affected patients. For an early diagnosis and a quickly intervention in treatment of X-ALD patients, it is necessary the implementation of program for neonatal screening of this pathology.

BIBLIOGRAPHY:

1. Mosser J, Douar AM, Sarde CO, Kioschis P, Feil R, Moser H, et al: Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. *Nature* 1993, 361:726–730
2. Singh I, Moser AE, Moser HW, Kishimoto Y: Adrenoleukodystrophy: impaired oxidation of very long chain fatty acids in white blood cells, cultured skin fibroblasts, and amniocytes. *Pediatr Res* 1984, 18:286–290.
3. Kemp S, Valianpour F, Mooyer PA, Kulik W, Wanders RJ: Method for measurement of peroxisomal very-long-chain fatty acid {beta}-oxidation in human skin fibroblasts using stable-isotope-labeled tetracosanoic acid. *Clin Chem* 2004, 50:1824–1826.
4. Moser HW, Moser AB, Frayer KK, Chen W, Schulman JD, O'Neill BP, et al: Adrenoleukodystrophy: increased plasma content of saturated very long chain fatty acids. *Neurology* 1981, 31:1241–1249.
5. Bezman L, Moser HW: Incidence of X-linked adrenoleukodystrophy and the relative frequency of its phenotypes. *Am J Med Genet* 1998, 76:415–419.
6. Laureti S, Casucci G, Santeusanio F, Angeletti G, Aubourg P, Brunetti P: X-linked adrenoleukodystrophy is a frequent cause of idiopathic Addison's disease in young adult male patients. *J Clin Endocrinol Metab*1996, 81:470–474.
7. Hsieh S, White PC: Presentation of primary adrenal insufficiency in childhood. *J Clin Endocrinol Metab* 2011, 96:E925–E928.

8. Christoph W., Florian S E., and Johannes B. The genetic landscape of X-linked adrenoleukodystrophy: inheritance, mutations, modifier genes, and diagnosis. *Appl Clin Genet*. 2015; 8: 109–121.
9. P. Aubourg, X-linked adrenoleukodystrophy, in: P.J. Vinken, C.W. Bruyn, H.W. Moser (Eds.), Handbook of Clinical Neurology, vol. 66, Elsevier, Amsterdam,1996, pp. 447–483.
10. D.J. Loes, S. Hite, H. Moser, A.E. Stillman, E. Shapiro, L. Lockman, R.E. Latchaw, W. Krivit, Adrenoleukodystrophy: a scoring method for brain MR observations, *AJNR Am. J. Neuroradiol.* 15 (1994) 1761–1766.
11. E.R. Melhem, P.B. Barker, G.V. Raymond, H.W. Moser, X-linked adrenoleukodystrophy in children: review of genetic, clinical, and MR imaging characteristics, *AJR Am. J. Roentgenol.* 173 (1999) 1575–1581
12. M. Barbier, A. Sabbagh, E. Kasper, M. Asheuer, O. Ahouansou, I. Pribill, S. Forss-Petter, M. Vidaud, J. Berger, P. Aubourg, CD1 gene polymorphisms and phenotypic variability in X-linked adrenoleukodystrophy, *PLoS One 7* (2012) e29872.
13. Shapiro, E. et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral Xlinked adrenoleukodystrophy. *Lancet* 356,2000. 713–718.
14. Miller, W. P. et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood 118, 2011. 1971–1978.
15. Aubourg, P. *et al.* Reversal of early neurologic and neuroradiologic manifestations of Xlinked adrenoleukodystrophy by bone marrow transplantation. *N. Engl. J. Med.* 322, 1990.1860–1866.
16. Peters, C. *et al.* Cerebral Xlinked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. *Blood 2004.* 104, 881–888.
17. Köhler, W. & Kühl, J. S. Hematopoietic stem cell transplantation for adult cerebral Xlinked adrenoleukodystrophy (P5.174). *Neurology 82(Suppl.),* 2014.10.
18. van Geel, B. M. et al. Hematopoietic cell transplantation does not prevent myelopathy in Xlinked adrenoleukodystrophy: a retrospective study. *J. Inherit. Metab*. Dis. 38, 2015. 359–361.
19. Moser, A. B. et al. A new dietary therapy for adrenoleukodystrophy: biochemical and preliminary clinical results in 36 patients. *Ann. Neurol.* 21,1987. 240–249.
20. Rizzo, W. B. et al. Adrenoleukodystrophy: dietary oleic acid lowers hexacosanoate levels. *Ann. Neurol.* 21,1987. 232–239.
21. Rasmussen, M., Moser, A. B., Borel, J., Khangoora, S. & Moser, H. W. Brain, liver, and adipose tissue erucic and very long chain fatty acid levels in adrenoleukodystrophy patients treated with glyceryl trierucate and trioleate oils (Lorenzo's oil). *Neurochem. Res.* 19, 1994,1073–1082.
22. Lopez-Erauskin, J. et al. Antioxidants halt axonal degeneration in a mouse model of Xadrenoleukodystrophy. *Ann. Neurol. 70 2011*, 84–92.
23. US National Library of Medicine. *ClinicalTrials.gov* http://www.clinicaltrials.gov/ct2/show/NCT01495260 (2014)
24. Vogel, B. H. *et al.* Newborn screening for Xlinked adrenoleukodystrophy in New York State: diagnostic protocol, surveillance protocol and treatment guidelines. *Mol. Genet. Metab.2015* 114, 599–603.
25. Turgeon, C. T. et al. Streamlined determination of lysophosphatidylcholines in dried blood spots for newborn screening of Xlinked adrenoleukodystrophy. *Mol. Genet. Metab.*2015 114, 46–50.
26. Engelen M, Ofman R, Dijkgraaf MGW, Hijzen M, van der Wardt LA, van Geel (XALD): clinical presentation and guidelines for diagnosis, followup and management. *Orphanet J. Rare Dis.* 2012*,* 7, 51.
27. Horn, M. A. et al. Screening for Xlinked adrenoleukodystrophy among adult men with Addison's disease. *Clin. Endocrinol. (Oxf.),*2013 .79, 316–320 (2013).
28. BM, et al: Lovastatin in X-linked adrenoleukodystrophy. *N Engl J M*ed 2010, 362:276–277.