Marie-Josée DURAN

De: Raymond, Gerald <raymond@kennedykrieger.org>
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PubMed Results

Items 1 - 10 of 10

1. J Neurol. 2012 Jan 5. [Epub ahead of print]

SOD2 as a potential modifier of X-linked adrenoleukodystrophy clinical phenotypes.

Brose RD, Avramopoulos D, Smith KD.

Source

McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA.

Abstract

X-linked adrenoleukodystrophy (XALD), a neurological disorder caused by mutations in the peroxisomal membrane protein gene ABCD1, presents as a rapidly progressing, inflammatory cerebral demyelination (cerebral cases) or a slowly progressing, distal axonopathy (non-cerebral cases). Specific ABCD1 defects do not explain this significant phenotypic variation. Patients have increased plasma and tissue very long chain fatty acid levels and increased cellular oxidative stress and oxidative damage. Superoxide dismutase 2 (SOD2), at candidate modifier locus 6q25.3, detoxifies superoxide radicals protecting against oxidative stress and damage. We tested an SOD2 variant C47T (Ala16Val) associated with reduced enzymatic activity as a potential modifier gene of cerebral demyelinating disease by comparing 117 cerebral XALD cases with 105 non-cerebral XALD cases. The hypoactive valine allele of the variant was associated with cerebral disease under a dominant model in the full data set (p = 0.04; ORT* = 1.90, 95% CI 1.01-3.56) and the non-childhood cerebral disease subset (p = 0.03; ORT* = 2.47, 95% CI 1.08-5.61). Three tag SNPs were genotyped to test for additional SNP or haplotype associations. A common haplotype, GTAC,

which included the SOD2 valine allele, was associated with cerebral disease in the full data set (p = 0.03; OR = 1.75, 95% CI 1.11-2.75) and the non-childhood cerebral disease subset (p = 0.008; OR = 2.20, 95% CI 1.27-3.83). There was no association between childhood cerebral XALD and the C47T variant or the GTAC haplotype. Thus, reduced SOD2 activity may contribute to the development of cerebral demyelination in adolescent and adult XALD patients.

PMID:
22218650

[PubMed - as supplied by publisher]

2. J Inherit Metab Dis. 2011 Dec 22. [Epub ahead of print]

A mixture of oleic, erucic and conjugated linoleic acids modulates cerebrospinal fluid inflammatory markers and improve somatosensorial evoked potential in X-linked adrenoleukodystrophy female carriers.

Cappa M, Bizzarri C, Petroni A, Carta G, Cordeddu L, Valeriani M, Vollono C, De Pasquale L, Blasevich M, Banni S.

Source

Unità Operativa di Endocrinologia, Ospedale Pediatrico Bambino Gesù, Roma, Italy.

Abstract

X-linked adrenoleukodystrophy is a rare inherited demyelinating disorder characterized by an abnormal accumulation of very long chain fatty acids, mainly hexacosanoic acid (26:0), due to a mutation of the gene encoding for a peroxisomal membrane protein. The only available, and partially effective, therapeutic treatment consists of dietary intake of a 4:1 mixture of triolein and trierucin, called Lorenzo's oil (LO), targeted to inhibit the elongation of docosanoic acid (22:0) to 26:0. In this study we tested whether, besides inhibiting elongation, an enhancement of peroxisomal beta oxidation induced by conjugated linoleic acid (CLA), will improve somatosensory evoked potentials and modify inflammatory markers in adrenoleukodystrophy females carriers. We enrolled five heterozygous women. They received a mixture of LO (40 g/day) with CLA (5 g/day) for 2 months. The therapeutic efficacy was evaluated by the means of plasma levels of 26:0, 26:0/22:0 ratio, modification of cerebrospinal fluid (CSF) inflammatory markers and somatosensory evoked potentials. Changes of fatty acid profile, and in particular CLA incorporation, were also evaluated in CSF and plasma. The results showed that CLA promptly passes the blood brain barrier and the mixture was able to lower both 26:0 and 26:0/22:0 ratio in plasma. The mixture improved somatosensory evoked potentials, which were previously found unchanged or worsened with dietary LO alone, and reduced IL-6 levels in CSF in three out of five patients. Our data suggest that the synergic activity of CLA and LO, by enhancing peroxisomal beta-oxidation and preventing 26:0 formation, improves the somatosensory evoked potentials and reduces neuroinflammation.

PMID:
22189598

[PubMed - as supplied by publisher]

Related citations

3. J Neuroinflammation. 2011 Oct 20;8:144.

Chitotriosidase as a biomarker of cerebral adrenoleukodystrophy.

Orchard PJ, Lund T, Miller W, Rothman SM, Raymond G, Nascene D, Basso L, Cloyd J, Tolar J.

Source

Department of Pediatrics, Program in Blood & Marrow Transplantation, University of Minnesota, Minneapolis, USA. orcha001@umn.edu.

Abstract

ABSTRACT:

BACKGROUND:

Adrenoleukodystrophy (ALD) is an X-linked peroxisomal disorder characterized by the abnormal beta-oxidation of very long chain fatty acids (VLCFA). In 35-40% of children with ALD, an acute inflammatory process occurs in the central nervous system (CNS) leading to demyelination that is rapidly progressive, debilitating and ultimately fatal. Allogeneic hematopoietic stem cell transplantation (HSCT) can halt disease progression in cerebral ALD (C-ALD) if performed early. In contrast, for advanced patients the risk of morbidity and mortality is increased with transplantation. To date there is no means of quantitating neuroinflammation in C-ALD, nor is there an accepted measure to determine prognosis for more advanced patients.

METHODS:

As cellular infiltration has been observed in C-ALD, including activation of monocytes and macrophages, we evaluated the activity of chitotriosidase in the plasma and spinal fluid of boys with active C-ALD. Due to genotypic variations in the chitotriosidase gene, these were also evaluated.

RESULTS:

We document elevations in chitotriosidase activity in the plasma of patients with C-ALD (n = 38; median activity 1,576 ng/mL/hr) vs. controls (n = 16, median 765 ng/mL/hr, p = 0.0004), and in the CSF of C-ALD patients (n = 38; median activity 4,330 ng/mL/hr) vs. controls (n = 16, median 0 ng/mL/hr, p < 0.0001). In addition, activity levels of plasma and CSF chitotriosidase prior to transplant correlated with progression as determined by the Moser/Raymond functional score 1 year following transplantation (p = 0.002 and < 0.0001, respectively).

CONCLUSIONS:

These findings confirm elevation of chitotriosidase activity in patients with active C-ALD, and suggest that these levels predict prognosis of patients with C-ALD undergoing transplantation.

PMCID: PMC3236018
Free PMC Article
PMID:
22014002
[PubMed - in process]
Related citations

4. Arch Neurol. 2011 Oct;68(10):1338-9.

Brain fludeoxyglucose F 18 positron emission tomography hypometabolism in magnetic resonance imaging-negative x-linked adrenoleukodystrophy.

Renard D, Castelnovo G, Collombier L, Kotzki PO, Labauge P.

Source

Department of Neurology, CHU, Hôpital Caremeau, Nîmes, France. dimitrirenard@hotmail.com
PMID:
21987553
[PubMed - indexed for MEDLINE]
Related citations

5. J Lipid Res. 2011 Nov;52(11):2056-69. Epub 2011 Sep 4.

HDAC inhibitor SAHA normalizes the levels of VLCFAs in human skin fibroblasts from X-ALD patients and downregulates the expression of proinflammatory cytokines in Abcd1/2-silenced mouse astrocytes.

Singh J, Khan M, Singh I.

Source

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Abstract

X-adrenoleukodystrophy (X-ALD) is a peroxisomal metabolic disorder caused by mutations in the ABCD1 gene encoding the peroxisomal ABC transporter adrenoleukodystrophy protein (ALDP). The consistent metabolic abnormality in all forms of X-ALD is an inherited defect in the peroxisomal β-oxidation of very long chain FAs (VLCFAs >C22:0) and the resultant pathognomic accumulation of VLCFA. The accumulation of VLCFA leads to a neuroinflammatory disease process associated with demyelination of the cerebral white matter. The present study underlines the importance of a potent histone deacetylase (HDAC) inhibitor, suberoylanilide hydroxamic acid (SAHA) in inducing the expression of ABCD2 [adrenoleukodystrophy-related protein (ALDRP)], and normalizing the peroxisomal β-oxidation, as well as the saturated and monounsaturated VLCFAs in cultured human skin fibroblasts of X-ALD patients. The expression of ELOVL1, the single elongase catalyzing the synthesis of both saturated VLCFA (C26:0) and monounsaturated VLCFA (C26:1), was also reduced by SAHA treatment. In addition, using Abcd1/Abcd2-silenced mouse primary astrocytes, we also examined the effects of SAHA in VLCFA-induced inflammatory response. SAHA treatment decreased the inflammatory response as expression of inducible nitric oxide synthase, inflammatory cytokine, and activation of NF-κB in Abcd1/Abcd2-silenced mouse primary astrocytes was reduced. These observations indicate that SAHA corrects both the metabolic disease of VLCFA as well as secondary inflammatory disease; therefore, it may be an ideal drug candidate to be tested for X-ALD therapy in humans.

PMCID: PMC3196237

[Available on 2012/11/1]
PMID:
21891797
[PubMed - in process]
Related citations

6. J Clin Pharm Ther. 2011 Jun;36(3):412-5. doi: 10.1111/j.1365-2710.2011.01267.x. Epub 2011 Apr 4.

New treatment of free-radical scavenger in adrenoleukodystrophy.

Kawashima H, Nishimata S, Ishii C, Yamanaka G, Kashiwagi Y, Takekuma K, Hoshika A, Watanabe Y.

Source

Department of Paediatrics, Tokyo Medical University, Tokyo, Japan. hisashi@tokyo-med.ac.jp

Abstract

WHAT IS KNOWN AND

OBJECTIVE:

Adrenoleukodystrophy (ALD) is an X-linked disorder and characterized by the accumulation of saturated very long-chain fatty acids. Treatment is still unsatisfactory. Our objective is to report on the effect of the free-radical scavenger, edaravone, in a patient with ALD.

CASE SUMMARY:

The patient was given edaravone intravenously twice. D-ROM in cerebral spinal fluid decreased dramatically, and a shortening of neuronal transmission time as estimated on somatosensory evoked potential was observed. After terminating the treatment, his symptoms progressively reappeared. WHAT IS NEW AND

CONCLUSION:

This is the first report of the use of edaravone in ALD. The drug is apparently effective in improving symptoms of ALD and should be evaluated more formally.

PMID:
21463348
[PubMed - indexed for MEDLINE]
Related citations

7. J Endocrinol Invest. 2011 Mar 7. [Epub ahead of print]

Is subclinical adrenal failure in Adrenoleukodystrophy/Adrenomyeloneuropathy (ALD/AMN)

reversible?

Cappa M, Bizzarri C, Giannone G, Aiello C, Di Biase A.

Source

Endocrinology Unit, Bambino Gesú Children's Hospital-IRCCS, Rome, Italy.

Abstract

Background: X-linked adrenoleukodystrophy/adrenomieloneuropathy (ALD/AMN) is a progressive neurodegenerative disorder due to mutations in the ABCD1 gene encoding the ABC transporter ALDP. Mutations in ALDP impair peroxisomal beta-oxidation of very long chain fatty acids (VLCFA), resulting in elevated levels of VLCFA in plasma, nervous system and adrenals. Lorenzo's oil, combined with VLCFApoor diet, normalizes plasma VLCFA within one month, but it does not prevent the progression of preexisting neurological symptoms. No previous study analyzed the effect of Lorenzo's oil therapy on adrenal function. Aim: to investigate short term effects of Lorenzo's oil, combined with VLCFA-poor diet, on adrenal function of AMN patients with early subclinical signs of adrenal failure. Subjects and Methods: Seven AMN subjects underwent VLCFA-restricted diet combined with Lorenzo'oil (45 ml/day orally), without steroid therapy, for 6 months. Results: All patients had elevated ACTH at baseline, and a significant reduction was evident after 6 months (median ACTH at baseline: 1300 pg/ml - range: 720-2100; median ACTH at 6 months: 186 pg/ml - range: 109-320, p: 0.0156). Cortisol was normal both at baseline and after 6 months. VLCFA dropped in all patients during the 6 month follow up, and no patient required glucocorticoid replacement therapy. Conclusions: Adrenal insufficiency in ALD/AMN is probably due to a defective adrenal response to ACTH, related to VLCFA accumulation with progressive disruption of the adrenal cell membrane functions. In an early phase, Lorenzo's oil therapy may be able to improve VLCFA clearance and restore a normal ACTH receptor activity, and hypoadrenalism may be potentially reversible.

PMID:
21399389
[PubMed - as supplied by publisher]

Related citations

8. Pediatr Neurol. 2011 Feb;44(2):143-6.

Evaluation of neuroinflammation in X-linked adrenoleukodystrophy.

Kumar A, Chugani HT, Chakraborty P, Huq AH.

Source

Department of Pediatrics and Neurology, Wayne State University School of Medicine, Children's Hospital of Michigan, Detroit Medical Center, Detroit, Michigan 48201, USA.

Abstract

We present findings of (11)C-[R]-PK11195 positron emission tomography in a child with X-linked adrenoleukodystrophy. (11)C-[R]-PK11195 is a radioligand with a high and specific affinity for peripheral benzodiazepine receptors, expressed by activated microglia in cases of neuroinflammation, and therefore it is applicable to the in vivo detection of neuroinflammation with positron emission tomography. (11)C-[R]-PK11195 positron emission tomography demonstrated increased tracer binding in

the occipital, parietal, and posterior temporal white matter, in the genu of the corpus callosum, the bilateral posterior thalami, most of the posterior limb of the internal capsule, the bilateral cerebral peduncles, and the brainstem, indicating underlying neuroinflammation. The rest of the brain, including the cerebral cortices and cerebellum, exhibited minimal (11)C-[R]-PK11195 binding. Our findings indicate significant neuroinflammation associated with white matter destruction in X-linked adrenoleukodystrophy, which can be visualized in vivo with an (11)C-[R]-PK11195 positron emission tomography scan. (11)C-[R]-PK11195 positron emission tomography may also help evaluate the inflammatory burden and follow-up of the disease evolution. This technique may be particularly useful for evaluating treatment response, which is not easy with other imaging modalities, after white matter is significantly and extensively damaged.

PMID:
21215916
[PubMed - indexed for MEDLINE]
Related citations

9. FEBS J. 2011 Jan;278(2):182-94. doi: 10.1111/j.1742-4658.2010.07947.x. Epub 2010 Dec 13.

Fatty acid omega-oxidation as a rescue pathway for fatty acid oxidation disorders in humans.

Wanders RJ, Komen J, Kemp S.

Source

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Abstract

Fatty acids (FAs) can be degraded via different mechanisms including α-, β- and ω-oxidation. In humans, a range of different genetic diseases has been identified in which either mitochondrial FA β-oxidation, peroxisomal FA β-oxidation or FA α-oxidation is impaired. Treatment options for most of these disorders are limited. This has prompted us to study FA ω-oxidation as a rescue pathway for these disorders, based on the notion that if the ω-oxidation of specific FAs could be upregulated one could reduce the accumulation of these FAs and the subsequent detrimental effects in the different groups of disorders. In this minireview, we describe our current state of knowledge in this area with special emphasis on Refsum disease and X-linked adrenoleukodystrophy.

PMID:
21156023
[PubMed - indexed for MEDLINE]
Related citations

10. J Neuroimmunol. 2010 Dec 15;229(1-2):204-11.

Invariant NKT cells in adrenoleukodystrophy patients and mice.

Gautron AS, Giquel B, Beaudoin L, Autrusseau E, Speak A, Platt F, Kemp S, Pujol A, Aubourg P, Lehuen A.

Source

INSERM U986, Hôpital Cochin/Saint-Vincent de Paul, Université Paris Descartes, Paris, France.

Abstract

X-linked adrenoleukodystrophy (X-ALD) is a severe neurological disease characterized by progressive demyelination within the CNS, adrenal insufficiency, and is associated with an accumulation of saturated very long chain fatty acids in plasma and tissues of patients. iNKT cells, a distinct lineage of T cells recognizing glycolipid antigens through CD1d molecules, exert immunoregulatory functions and can prevent various immune mediated-pathologies. In ALD patients, but not in ALD deficient mice, iNKT cell frequency and CD1d expression on the surface of B cells are slightly decreased. However, such minor differences might not influence the pathogenesis of the disease.

PMID:
20920830
[PubMed - indexed for MEDLINE]

Related citations