
   **Iron deposition surrounding the hepatic veins of cirrhotic patients on MRI.**

   Horowitz JM, Nikolaidis P, Chen ZM, Siegelman E, Garg A, Feng C, Miller FH.

   Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA. Jhorowitz77@gmail.com.

   **PURPOSE:** To provide the first description of a pattern of iron deposition surrounding the hepatic veins in patients with alcoholic cirrhosis and postulate the reason for these findings.

   **MATERIALS AND METHODS:** Two institutions' teaching files were searched for abdominal MRI studies between January 2003 and April 2009 which showed iron deposition within the liver surrounding the hepatic veins. MRI exams were reviewed by two radiologists for iron deposition and signs of portal hypertension. Liver explant pathology reports were also reviewed.

   **RESULTS:** Four patients with alcoholic cirrhosis demonstrated perihepatic vein low signal intensity on T1 gradient echo images correlating with iron overload confirmed at histopathologic evaluation of explanted livers.

   **CONCLUSION:** This is the first described uncommon distribution of iron deposition surrounding the hepatic veins. This pattern is well seen on in-phase T1 gradient echo sequences because of the T2* effects in this sequence. J. Magn. Reson. Imaging 2011;33:598-602. © 2011 Wiley-Liss, Inc.

   PMID: 21563243 [PubMed - in process]


   **Caffeic acid inhibits the formation of 1-hydroxyethyl radical in the reaction mixture of rat liver microsomes with ethanol partly through its metal chelating activity.**

   Ikeda H, Kimura Y, Masaki M, Iwahashi H.

   Department of Chemistry, Wakayama Medical University, 580 Mikazura, Wakayama 641-0011, Japan.

   Effect of caffeic acid on the formation of 1-hydroxyethyl radicals via the microsomal ethanol-oxidizing system pathway was examined. The electron spin
resonance spin trapping showed that 1-hydroxyethyl radicals form in the control reaction mixture which contained 0.17 M ethanol, 1 mg protein/ml rat river microsomes, 0.1 M a-(4-pyridyl-1-oxide)-N-tert-butylnitroline, 5 mM nicotinamide adenine dinucleotide phosphate and 30 mM phosphate buffer (pH 7.4). When the electron spin resonance spectra of the control reaction mixtures with caffeic acid were measured, caffeic acid inhibited the formation of 1-hydroxyethyl radicals in a concentration dependent manner. Gallic acid, dopamine, l-dopa, chlorogenic acid and catechin also inhibited the formation of 1-hydroxyethyl radicals. Above results indicated that the catechol moiety is essential to the inhibitory effect. Caffeic acid seems to chelate of iron ion at the catechol moiety. Indeed, the inhibitory effect by caffeic acid was greatly diminished in the presence of desferrioxamine, a potent iron chelator which removes iron ion in the Fe (III)-caffeic acid complex. Since Fe (III)-desferrioxamine complex is active for the 1-hydroxyethyl radicals formation, caffeic acid inhibits the formation of 1-hydroxyethyl radicals in the reaction mixture partly through its metal chelating activity.

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3.  


**Mechanism and Kinetics of Ligand Exchange between Ferric Citrate and Desferrioxamine B.**

Ito H, Fujii M, Masago Y, Yoshimura C, Waite TD, Omura T.

Department of Civil and Environmental Engineering, Tohoku University, Aoba 6-6-06 Aobaku, Sendai 980-8579, Japan.

The kinetics of ligand exchange between ferric citrate and desferrioxamine B (DFB) was investigated at pH 8.0 and high citrate/Fe molar ratios (500-5000) with particular attention given to understanding the precise mechanism of ligand exchange. Ferric citrate complexes present in a test solution and therefore involved in the reaction with the incoming ligand (DFB) were initially examined by evaluating ferric citrate speciation on the basis of published thermodynamic constants. The speciation analysis indicated that mononuclear (mono- and dicitrate) ferric complexes are the major species responsible for the ligand exchange with DFB under the conditions examined in the present work. Given the tendency of DFB to adjunctively associate with the ferric citrate complexes, we propose a kinetic model containing the following three mechanisms: (i) direct association of DFB to the ferric dicitrate complex prior to any dissociation of citrate molecules from the Fe center, (ii) adjunctive association of DFB toward ferric monocitrate complex following dissociation of one molecule of citrate from...
the parent complex, and (iii) complexation of hydrated Fe by DFB after sequential
dissociation of two molecules of citrate from the Fe center. Overall rates for
the ligand exchange were determined by spectrophotometrically monitoring the
formation of ferrioxamine B. Further analysis in quantifying the rate of each
mechanism by use of published and determined rate constants of relevant elemental
reactions suggested that the first and second mechanisms were significant under
our experimental conditions where [Cit] ≫ [DFB] with the relative importance of
these two pathways depending on citrate concentration.

PMID: 21561126 [PubMed - as supplied by publisher]


**Short-term Toxicity Study of ST-20 (NSC-741804) by Oral Gavage in
Sprague-Dawley Rats.**

Terse PS, Johnson JD, Hawk MA, Ritchie GD, Ryan MJ, Vasconcelos DY, Contos DA,
Perrine SP, Peggins JO, Tomaszewski JE.

National Cancer Institute, Bethesda, Maryland, USA.

ST-20 (sodium 2,2-dimethylbutyrate) is a potential therapeutic agent for
treatment of β-thalassemia and sickle cell disease. A subchronic oral toxicity
study was conducted in Sprague-Dawley rats (10/sex/dose) at gavage dosages of 0
(vehicle control), 200, 600, or 1,000 mg/kg, once daily for up to 15 days
followed by a 14-day recovery. Ataxia (females), rough coat/thin appearance
(males), and decreased body weights were observed at 1,000 mg/kg. Functional
observational battery (FOB) deficits were observed more frequently in females and
included decreased body tone, rectal temperature, emotional reactivity,
neuromotor-neuromuscular activity (as exhibited by a deficit in visual/tactile
placing accuracy, ataxia, hind limb dragging, and decreased grip strength), and
rearing. ST-20 caused a decrease in WBC/RBC counts and RBC parameters; increase
in reticulocytes and red cell inclusion bodies; decrease in total protein,
globulin, and glucose; and increase in AG ratio. Micronucleated polychromatic
erthrocytes of the bone marrow increased significantly in males at 1,000 mg/kg.
Mean liver and kidney weights increased, and hepatocellular hypertrophy was
observed in males at 1,000 mg/kg. Toxicologic findings were fully recovered
during the 14-day recovery period. In conclusion, the no-observed adverse effect
level for FOB and general toxicity was 200 mg/kg following gavage administration
of ST-20 for up to 15 consecutive days.

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**ALTERED ZINC TRANSPORT DISRUPTS MITOCHONDRIAL PROTEIN PROCESSING/IMPORT IN FRAGILE X-ASSOCIATED TREMOR/ATAXIA SYNDROME.**


Department of Molecular Biosciences, School of Veterinary Medicine.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that affects individuals who are carriers of small CGG premutation expansions in the FMR1 gene. Mitochondrial dysfunction was observed as an incipient pathological process occurring in individuals who do not display overt features of FXTAS (1). Fibroblasts from premutation carriers had lower OXPHOS capacity (35% of controls) and Complex IV activity (45%), and higher precursor-to-mature ratios (P:M) of nDNA-encoded mitochondrial proteins (3.1-fold). However, fibroblasts from carriers with FXTAS symptoms presented higher FMR1 mRNA expression (3-fold) and lower Complex V (38%) and aconitase activities (43%). Higher P:M ratios of ATPB and frataxin were also observed in cortex from patients that died with FXTAS symptoms. Biochemical findings observed in FXTAS cells (lower mature frataxin, lower Complex IV and aconitase activities) along with common phenotypic traits shared by Friedreich's ataxia and FXTAS carriers (e.g., gait ataxia, loss of coordination) are consistent with a defective iron homeostasis in both diseases. Higher P:M ratios, and lower ZnT6 and mature frataxin protein expression suggested defective zinc and iron metabolism arising from altered ZnT protein expression, which in turn impairs the activity of mitochondrial Zn-dependent proteases, critical for the import and processing of cytosolic precursors such as frataxin. In support of this hypothesis, Zn-treated fibroblasts showed a significant recovery of ATPB P:M, ATPase activity, and doubling time; whereas Zn and desferrioxamine extended these recoveries and rescued Complex IV activity.

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*Database: PubMed, Embase*

*Keywords: deferiprone, 30652-11-0, desferrioxamine, deferoxamine, desferal, deferasirox, (iron + sickle) iron chelation, iron chelators, iron overload, thalass*, 1,2 dimethyl-3-hydroxypyridin-4-one, ICL670*, Exjade*

**Induction of hypoxia inducible factor (HIF-1α) in the rat kidneys by iron chelation with the hydroxypyridinone, CP94.**

Baek JH, Reiter CE, Manalo DJ, Buehler PW, Hider RC, Alayash AI.

Laboratory of Biochemistry and Vascular Biology, Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA.

Hypoxia inducible factor (HIF-1α) is a master regulator of tissue adaptive responses to hypoxia whose stability is controlled by an iron containing prolyl hydroxylase domain (PHD) protein. A catalytic redox cycle in the PHD's iron center that results in the formation of a ferryl (Fe(+4)) intermediate has been reported to be responsible for the hydroxylation and subsequent degradation of HIF-1α under normoxia. We show that induction of HIF-1α in rat kidneys can be achieved by iron reduction by the hydroxypyridin-4-one (CP94), an iron chelator administered intraperitoneally in rats. The extent of HIF protein stabilization as well as the expression of HIF target genes, including erythropoietin (EPO), in kidney tissues was comparable to those induced by known inhibitors of the PHD enzyme, such as desferrioxamine (DFO) and cobalt chloride (CoCl(2)). In human kidney cells and in vitro PHD activity assay, we were able to show that the HIF-1α protein can be stabilized by addition of CP94. This appears to inactivate PHD; and thus prevents the hydroxylation of HIF-1α. In conclusion, we have identified the inhibition of iron-binding pocket of PHD as an underlying mechanism of HIF induction in vivo and in vitro by a bidentate hydroxypyridinone.

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**Antiphospholid antibody syndrome and Hb E/Beta thalassemia disease post-allogeneic stem cell transplantation.**

Sirachainan N, Pakakasama S, Hongeng S, Chuansumrit A, Tuntiyatorn L, Vilaiyuk S.

Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand. rasrb@mahidol.ac.th.

We report a 10-year-old male with Hb E/Beta thalassemia disease who developed chronic graft-versus-host disease (cGVHD) of antiphospholipid antibody syndrome...
after successful allogeneic stem cell transplantation (SCT). He exhibited a recurrent ischemic stroke on day 368 post-SCT while on cyclosporine A, azathioprine, and prednisolone. The immunosuppressive agents were switched to pulse methylprednisolone, tacrolimus, mycophenolate mofetil, and enoxaparin, but the patient was more confused. An additional plasma exchange which was aimed at the immediate removal of autoantibody was performed with a good response. The symptoms rapidly disappeared except for the complex partial seizure which persisted until seven years post-SCT. Pediatr Blood Cancer 2011;57:153-156. © 2011 Wiley-Liss, Inc.

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Iron-related MRI images in patients with pantothenate kinase-associated neurodegeneration (PKAN) treated with deferiprone: Results of a phase II pilot trial.


Unit of Child Neurology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy.

BACKGROUND: The safety and efficacy of the oral iron-chelating agent deferiprone on magnetic resonance pallida iron concentration and on clinical status were investigated in 10 patients affected by pantothenate kinase-associated neurodegeneration. METHODS: Nine patients (age range, 7-39 years) completed the study. RESULTS: A significant median reduction in globus pallidus iron content as assessed by T2* relaxometry (and calculated R2* maps; P = .008) was observed at the end of the study. None of the patients demonstrated a change in clinical status as assessed by the Burke-Fahn and Marsden Dystonia Rating scales and by a health-related quality-of-life scale. Deferiprone was well tolerated, and no serious adverse events occurred. CONCLUSIONS: Future trials assessing the clinical efficacy of chelating therapy should consider early symptomatic patients and a longer treatment period. © 2011 Movement Disorder Society.

PMID: 21557313 [PubMed - as supplied by publisher]

**The relationship between indices of iron status and selected anthropometric cardiovascular disease risk markers in an African population: the THUSA study.**

Aderibigbe OR, Pisa PT, Mamabolo RL, Kruger HS, Vorster HH.

Centre of Excellence for Nutrition, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa.

There is evidence that certain indices of iron status are associated with anthropometric measures, which are used independently as markers of cardiovascular disease (CVD) risk. This study examined whether this association exists in an African population. The study was a cross-sectional comparative study that examined a total of 1854 African participants. Ferritin was positively associated with body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), percentage body fat and subscapular skinfold thickness. Serum ferritin concentration was higher in the high-WHR category than the normal-WHR category for both genders. Additionally, WC and WHR increased with increasing ferritin concentrations in both genders. Serum iron was lower in the obese than the normal-weight and pre-obese women only. In this population-based study, increased serum ferritin concentrations associated positively with increased WHR and WC, indicating that individuals or populations at risk of iron overload as defined by high serum ferritin concentrations may be at a greater risk of developing CVD.

PMID: 21556462 [PubMed - as supplied by publisher]


**The impact of two different doses of chelating therapy (Deferasirox) on Echocardiographic Tissue Doppler Indices in Patients with Thalassemia Major.**

Garadah TS, Mahdi N, Kassab S, Abu-Taleb A, Shoroqi I, Alawadi AH.

Cardiac Unit, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain Royal Colleges of Surgeons in Ireland, Medical University of Bahrain, Kingdom of Bahrain Department of Family and Community Medicine, College of Medicine and Medical Sciences, Arabian Gulf University, Kingdom of Bahrain.
Background: Chelating therapy in transfusion-dependent patients with β-thalassemia major (β-TM) is mandatory to reduce the toxic effect of iron on the myocardium. Aim: To evaluate the impact of low and high dose of oral chelating therapy (deferasirox) on pulsed and tissue echocardiographic indices in patients with β-TM. Methods: This interventional study conducted on patients with transfusion-dependent β-TM (n =38) on Deferasirox 20 mg/kg/day medication, group (DFX- 20) for at least 6 months, followed by administration of a higher dose of Deferasirox, 40 mg/kg/day, group (DFX- 40) for another 6 months. Pulsed and tissue Doppler echocardiography carried out at the beginning and the end of treatment interval (6 months) for both groups, with monthly blood analysis of serum ferritin, alanine transaminase, hemoglobin, and creatinine. An age matched control group of 38 patients was evaluated for echo Doppler blood analysis.

Results: Patients of group DFX-40 compared with group DFX-20, the tissue Doppler echocardiogram showed lower E/Em ratio (16.01±2.85 vs. 19.68±2.81, p<0.05), higher systolic wave velocity (Sm) (5.87 ±1.40 vs. 4.80±1.20 p<0.05), and higher early diastolic wave (Em) velocity (4.25±1.70 vs. 3.50±1.80, P<0.05) respectively. Patients in group DFX 20, compared with control group had M-Mode echo with thicker LV septal wall (P<0.001) and posterior wall (P<0.01), higher LVEDD index (P<0.05). The pulsed Doppler echocardiogram showed a higher LV transmital E-wave velocity (p<0.05), higher E/A ratio (P<0.01) and the duration of deceleration time (DT) was significantly shorter (P<0.01). There were no significant changes observed in the left ventricle ejection fraction percentage (LVEF %) or fractional shortening (FS) between both treatment groups. Serum ferritin was significantly lower in DFX-40 group compared with DFX-20 β-TM group (338 There was a significant positive correlation between the serum ferritin and the E/Em ratio (r = 0.31, P< 0.001). The tricuspid valve velocity was significantly higher in β-TM patients compared with the control group (P<0.05).

Conclusion: The increment of oral deferasirox as chelating therapy in β-TM patients to 40mg/kg/day over 6 months duration showed a significant increments of systolic and diastolic tissue Doppler velocities with a significant reduction of E/Em ratio in comparison with 20mg/kg/day. There were no changes of left ventricle ejection fraction. A longer duration of follow-up may be justified in such group of patients.

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Might the association between gamma-glutamyltransferase and arterial stiffness be mediated by iron overload?

Mascitelli L, Goldstein MR.
Comando Brigata Alpina 'Julia', Medical Service, 8 Via S. Agostino, Udine, 33100, Italy Fountain Medical Court, 9410 Fountain Medical Court, Suite A-200, Bonita Springs, FL 34135, USA.

PMID: 21554374 [PubMed - as supplied by publisher]


**Biochemical and histological liver changes occurred after iron supplementation and possible remediation by garlic consumption.**

Ghorbel H, Feki I, Friha I, Khabir AM, Boudawara T, Boudawara M, Sayadi S.

Laboratoire des Bioprocédés Environnementaux, Pôle d'excellence régional AUF (PER-LBP), Center de biotechnologie de Sfax (CBS), Université de Sfax, BP:1177, 3038, Sfax, Tunisia, ghorbelh1@yahoo.fr.

Iron liver excess is associated to biochemical and histological liver perturbations. Our aim was to know even if fresh garlic consumption can remediate these problems. Three groups of rats were utilized: control group A, iron overload group B and garlic and iron overload group C. Important morphological and biochemical modifications were obtained in group B rats comparatively to control group A. Indeed, body and liver weights and liver iron contents increased, respectively, by 12.5 ± 0.06%; 17 ± 0.25% and 35 ± 0.11% comparatively to controls. Radical cation scavenging ability in liver cytosol of group B rats was significantly low (54 ± 0,1%) in comparison to group A. Garlic consumption allowed the group C to achieve an increase by 46 ± 0,11 and 75 ± 0,14% of total antioxidant capacity comparatively to group A and B rats. For the serum ALAT, ASAT, triglyceride and LDH levels, they increased in iron-treated rats, respectively, by 25 ± 0.21; 15 ± 0.12; 30 ± 0.14 and 22 ± 0.16% comparatively to controls. These perturbations were accompanied by deep histological changes. After food fresh garlic supplementation, we had found a deep regulation of all modified parameters showing a hepatoprotective effect of garlic against iron liver excess. Garlic chemical compounds have curative effects on iron liver excess.

PMID: 21553301 [PubMed - as supplied by publisher]

**Should we screen for hereditary hemochromatosis in healthy Lebanese: a pilot study.**

Mahfouz RA, Sarieddine DS, Charafeddine KM, Abdul Khalik RN, Cortas NK, Daher RT.

Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, P.O. Box 11-0236, Beirut, 1107-2020, Lebanon.

Hereditary hemochromatosis (HHC) is a genetic disorder of iron metabolism characterized by abnormal accumulation of iron that may lead to organ damage and death. Diagnosis is usually based on various genetic and phenotypic criteria. The study goals were to perform mutation analysis for 18 different mutations associated with HHC in healthy Lebanese, determine their allele frequency, and compare iron-overload status in identified carriers versus those found to be wild-type for mutations analyzed. 116 healthy adults (59 males and 57 females) underwent DNA testing for 18 different HHC mutations, and biochemical testing for percent transferrin saturation (%TS) and ferritin. C282Y mutation was not detected. Only H63D mutation (rs1799945) was found with an overall carrier frequency of 25.8% (24.1% heterozygous and 1.7% homozygous). %TS and ferritin differed significantly between genders. %TS and ferritin were significantly higher in males with H63D mutation when compared to males with wild-type (P = 0.001, 0.019; respectively); but not in females. The proportion of subjects with increased %TS and serum ferritin was not statistically different between those with H63D mutation and the wild-type in either gender. In addition, none of the subjects had concurrent increase in %TS and ferritin. In conclusion, the H63D carrier frequency in healthy Lebanese is comparable to other populations in the region, and it does not result in significant biochemical iron overload. Moreover, in the absence of the C282Y mutation, genetic screening for HHC is not recommended according to this preliminary study in healthy Lebanese.

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**A 6-year-old Girl with Hemoglobin H Disease.**

Ueda T, Migita M, Yamanishi M, Maeda M, Harano K, Fukunaga Y.

Department of Pediatrics, Graduate School of Medicine, Nippon Medical School.
Hemoglobin H (HbH) disease is the severe nonfatal form of α-thalassemia syndrome. It is usually caused by molecular defects of 3 of 4 α-globin genes (α/-α) which cause α-globin expression to be decreased. HbH disease is rare in Japan. Here, we report on a 6-year-old girl with HbH disease who had profound hypochromic and microcytic anemia. Analysis of the α-globin genes of the patient's family showed that the father, who was Japanese, had an abnormal gene with a 3.7-kb deletion (-α(3.7)/αα), and the mother, who was Filipino, had a deletion removing both α-globin genes of the Filipino type (-(FIL)/αα). Neither parent had anemia. The patient was found to have HbH disease with a heterozygous genetic abnormality (-(FIL)/-α(3.7)). Recently, the number of marriages of Japanese to natives of areas where thalassemia is epidemic has increased. Therefore, the incidence of HbH disease can be expected to increase in Japan. Long-term follow-up will be needed to evaluate the long-term complications and to improve the quality of life of patients with HbH disease.

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15. Neuropharmacology. 2011 Apr 23. [Epub ahead of print]

Myricetin attenuated MPP(+)‐induced cytotoxicity by anti‐oxidation and inhibition of MKK4 and JNK activation in MES23.5 cells.

Zhang K, Ma Z, Wang J, Xie A, Xie J.

Department of Physiology, Shandong Provincial Key Laboratory of Pathogenesis and Prevention of Neurological Disorders and State Key Disciplines: Physiology, Medical College of Qingdao University, Qingdao 266071, China.

Increasing evidence suggests that oxidative stress may be implicated in the degeneration of dopaminergic neurons in Parkinson's disease (PD), and anti-oxidation have been shown to be effective to PD treatment. Myricetin has been reported to have the biological functions of anti-oxidation, anti-apoptosis, anti-inflammation and iron-chelation. The aim of the present study is to investigate the neuroprotective effect of myricetin on 1-methyl-4-phenylpyridinium (MPP(+))-treated MES23.5 cells and the underlying mechanisms. The results showed that myricetin treatment significantly attenuated MPP(+)-induced cell loss and nuclear condensation. Further experiments demonstrated that myricetin could suppress the production of intracellular reactive oxygen species (ROS), restore the mitochondrial transmembrane potential (▵Ψm), increase Bcl-2/Bax ratio and decrease caspase-3 activation that induced by MPP(+). Furthermore, we also showed myricetin decreased the phosphorylation of mitogen-activated protein kinase (MAPK) kinase 4 (MKK4) and c-Jun N-terminal kinase (JNK) caused by MPP(+). These results suggest that myricetin protected the...
MPP(+-) treated MES23.5 cells by anti-oxidation and inhibition of MKK4 and JNK activation.

PMID: 21549720 [PubMed - as supplied by publisher]


**G6PD A-variant influences the antibody responses to Plasmodium falciparum MSP2.**


Institut de Recherche pour le Développement (IRD), Unité Mixte de Recherche (UMR) 216 « Mère et enfant face aux infections tropicales », 75006 Paris, France; Faculté de Pharmacie, Université Paris Descartes, Paris 75270, France; Institut des Sciences Biomédicales Appliquées, Cotonou, Benin; Laboratoire de Parasitologie, Faculté des Sciences de la Santé, Cotonou, Benin.

High antibody levels directed to Plasmodium falciparum merozoite surface proteins (MSP), including MSP2, as well as genetically related red blood cell defects, have previously been found to be associated with protection against malaria. Here, our main objective was to study the changes in MSP2-specific total IgG, IgG1 and IgG3 responses during a malaria transmission season in order to assess the impact of sickle-cell, α(+) -thalassemia and G6PD variants on antibody kinetics. Repeated parasitological assessments of a cohort of children were conducted during an 8-month period. Antibody responses to recombinant MSP2/3D7 and MSP2/FC27 proteins were measured at the beginning and at the end of transmission season. We found that (i) the period of last Plasmodium falciparum infection during the transmission season was associated with IgG3 anti-MSP2 change. Compared to the IgG3 levels of children infected in January 2003 (end of transmission season), the IgG3 level of children decreased with the length of the period without infection, (ii) G6PD A- carriers had a lower increase of IgG3 levels to MSP2/FC27 and MSP2/3D7 during the transmission season than the noncarriers. This latter finding is suggestive of qualitative and/or quantitative reduction of exposure to malarial antigens related to this genetic variant, leading to weaker stimulation of specific antibody responses. We speculate that cell-mediated immune activity may explain the clinical protection afforded by this genetic trait.

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**Split chimerism between nucleated and red blood cells after bone marrow transplantation for haemoglobinopathies.**

Andreani M, Testi M, Battarra M, Lucarelli G.

Laboratory of Immunogenetics; IME Foundation at Polyclinic of Tor Vergata Foundation; Rome, Italy.

Previous studies have shown that a stable presence of both donor and recipient haematopoietic derived cells after allogeneic haematopoietic stem cell transplantation (HSCT) occurs in approximately ten percent of the patients affected by β-Thalassemia. Once achieved this condition, defined as persistent mixed chimerism (PMC), the patients do not require additional red blood cells (RBCs) support and, regardless of the presence in some cases of an extremely low percentage of donor-derived nucleated cells, they are clinically cured by an incomplete, but functional graft. Most of the published papers have, however, investigated the impact of donor engraftment in the nucleated cells rather than in the mature erythrocytes. We have recently published a paper showing that in four long-term transplanted patients affected by hemoglobinopathies, characterized by the presence of few donor engrafted nucleated cells both in the peripheral blood and in the bone marrow—the majority of the erythrocytes were of donor origin. Moreover we showed that the proportion of donor-derived erythroid precursors, determined by analyzing singularly picked-up burst-forming unit erythroid colonies, was equivalent to that observed in the mature nucleated cells rather than in the red blood cells. These results suggest that in patients characterized by the presence of PMC after HSCT a selective advantage of the donor erythroid precursors maturation might successfully contrast the problems bound to the recipient ineffective erythropoiesis. When genetically modified HSCT will be a possible option for treating Thalassemia Major, the co-existence of the repaired cells with those still expressing the genetic defect will be an expected scenario, not in an allogeneic, but in an autologous environment.

PMCID: PMC3084953 [Available on 2012/1/1]
PMID: 21547033 [PubMed]


**Liver abscess in children: A 10-year single centre experience.**

Salahi R, Dehghani SM, Salahi H, Bahador A, Abbasy HR, Salahi F.
Transplant Research Center, Shiraz, Iran.

Background/Aim: Although liver abscess is more prevalent in developing countries than in developed countries, there is scant data about the characteristics of pediatric liver abscess in our region. We aimed to analyze the characteristics of pediatric liver abscess in our region and compare these with those of developed countries. Materials and Methods: The clinical features, laboratory, imaging, microbiologic findings, management strategy, and final outcome were extracted from the patients' records retrospectively. Results: There were 18 cases of liver abscess including 16 pyogenic liver abscess, one amebic liver abscess and one candida liver abscess. Fever and abdominal pain were the most common clinical findings and leukocytosis was the most common laboratory finding. The most predisposing factors of liver abscess were immune deficiency, minor thalassemia. Origin of liver abscess was appendicitis in two patients, the rest were considered as cryptogenic. While one patient was treated with antibiotics alone, five cases were taken for open drainage, and 12 cases were treated with percutaneous aspiration. Percutaneous aspiration failed in two patients who were later taken for open drainage, with an overall mortality rate of 5.5%.

Conclusion: The overall characteristics of liver abscess in children in our society are not so different from developed countries. However, in contradiction to cases reported in developed countries, most cases of liver abscess were seen in healthy patients in our centre. Moreover, liver abscess was reported in our patients at a younger age and was more commonly seen in male children. Mortality rate was similar to that of developed countries.

PMID: 21546724  [PubMed - in process]


**Predictors of osteoclast activity in sickle cell disease patients.**


Howard University, USA;

Background. Bone changes are common in sickle cell disease, but the pathogenesis is not fully understood. Tartrate-resistant acid phosphatase (TRACP) type 5b is produced by bone-resorbing osteoclasts. In other forms of hemolytic anemia, increased iron stores are associated with osteoporosis. We hypothesized that transfusional iron overload would be associated with increased osteoclast
activity in sickle cell disease patients. Design and Methods. We examined
tartrate-resistant acid phosphatase 5b concentrations in sickle cell disease
patients and normal controls of similar age and sex distribution at steady state.
Serum tartrate-resistant acid phosphatase 5b concentration was measured using an
immunocapture enzyme assay and plasma concentrations of other cytokines were
assayed by the Bio-Plex suspension array system. Tricuspid regurgitation
velocity, an indirect measure of systolic pulmonary artery pressure, was
determined by echocardiography. Results. Tartrate-resistant acid phosphatase 5b
concentrations were higher in 58 adult sickle cell disease patients than 22
controls (medians of 4.4 vs. 2.4 U/L, P=0.0001). Among sickle cell disease
patients, tartrate-resistant acid phosphatase 5b independently correlated with
blood urea nitrogen (standardized beta=0.40, P=0.003), interleukin-8
(standardized beta=0.30, P=0.020), and chemokine C-C motif ligand 5 (standardized
beta=-0.28, P=0.031), but not serum ferritin concentration. Frequent blood
transfusions (>10 units in life time) were not associated with higher
tartrate-resistant acid phosphatase 5b in multivariate analysis. There were
strong correlations among tartrate-resistant acid phosphatase 5b, alkaline
phosphatase and tricuspid regurgitation velocity (r>0.35, P<0.001). Conclusion.
Sickle cell disease patients have increased osteoclast activity as reflected in
serum tartrate-resistant acid phosphatase 5b concentrations. Our results may
support a potential role of inflammation rather than increased iron stores in
stimulating osteoclast activity in sickle cell disease patients. The positive
relationships among tartrate-resistant acid phosphatase 5b, alkaline phosphatase
and tricuspid regurgitation velocity raise the possibility of a common pathway in
the pulmonary and bone complications of sickle cell disease.

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[Posttransfusion iron overload].

[Article in Polish]

Korsak J.

Zaklad Transfuzjologii Klinicznej Wojskowego Instytutu Medycznego w Warszawie.
jkorsak@wim.mil.pl

Patients receiving red cell concentration regularly are liable to develop iron
overload. The characteristic feature of this condition is higher than normal
generalized iron depositing. Iron excess initially is deposited in the liver,
reticuloendothelial system, and consequently in such organs as the heart and
endocrine glands. Humans do not possess mechanisms to excrete the excess of this metal. Patients who have undergone long time hemotherapy develop manifestations of diabetes, liver cirrhosis or cardiomyopathy; the most common cause of death is heart failure. Posttransfusion iron overload is observed most often in patients with thalassemia, aplastic and hemolytic syndromes and with syderoplastic anemias. An interesting fact is that numerous and long time transfusions in patients with chronic bleeding do not results in iron overload. Each transfused unit of red cell concentrate delivers approximately 250 mg of iron, thus iron accumulation is an inevitable effect of long time red cell concentrate therapy. Excessive iron intake manifests clinically when the total iron level reaches 400-1000 mg/kg b.m. The clinical picture resulting from posttransfusion iron overload includes dark skin, liver cirrhosis and circulatory disorders in the form of arrhythmia and insufficiency (of left ventricle, particularly). Iron overload can be treated but it is better to prevent it by administering chelating drugs. These compounds have high affinity and specificity to iron. They eliminate it with urine in the form of a bound complex. The use of chelating drugs is recommended when around 20 red cell concentrate units have been transfused and the serum ferritin level is about 1000 microg/ml.

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[Endocrinological disorders in a patient with thalassemia mayor.]

[Article in Spanish]

Pavón de Paz I, Guijarro de Armas MG, Monteserín Monteserín C, Martín Boizas R, Civantos Modino S, Montaño Martínez JM, Iglesias Bolaños P.

Servicio de Endocrinología, Hematología y Radiodiagnóstico, Hospital Universitario de Getafe, Getafe, Madrid, España.

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Determination of fetal chromosome aberrations from fetal DNA in maternal blood: has the challenge finally been met?

Hahn S, Lapaire O, Tercanli S, Kolla V, Hösli I.
Laboratory for Prenatal Medicine, Department of Biomedicine / Department of Obstetrics and Gynecology, University Hospital Basel, Switzerland.

The analysis of cell-free fetal nucleic acids in maternal blood for prenatal diagnosis has been transformed by several recent profound technology developments. The most noteworthy of these are 'digital PCR' and 'next-generation sequencing' (NGS), which might finally deliver the long-sought goal of noninvasive detection of fetal aneuploidy. Recent data, however, indicate that NGS might even be able to offer a much more detailed appraisal of the fetal genome, including paternal and maternal inheritance of point mutations for mendelian disorders such as β-thalassaemia. Although these developments are very exciting, in their current form they are still too complex and costly, and will need to be simplified considerably for their optimal translation to the clinic. In this regard, targeted NGS does appear to be a step in the right direction, although this should be seen in the context of ongoing progress with the isolation of fetal cells and with proteomic screening markers.

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23. Virulence. 2011 May 1;2(3). [Epub ahead of print]

*Deferasirox lacks in vitro activity against Fusarium and Scedosporium species and black molds.*

Kontoyiannis DP.

Department of Infectious Diseases; Infection Control and Employee Health; The University of Texas MD Anderson Cancer Center; Houston, TX USA.

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ENTREZ EMBASE LITERATURE REVIEW (1 NEW ARTICLE(S))


The heart in Friedreich’s Ataxia: Basic findings and clinical implications

Payne R.M.

Friedreich’s Ataxia is the most common inherited ataxia in man. It is a mitochondrial disease caused by severely reduced expression of the iron binding protein, frataxin. A large GAA triplet expansion in the human FRDA gene encoding this protein inhibits expression of this gene. It is inherited in an autosomal recessive pattern and typically diagnosed in childhood. The primary symptoms include severe and progressive neuropathy, and a hypertrophic cardiomyopathy that may cause death. The cardiomyopathy is difficult to treat and is frequently associated with arrhythmias, heart failure, and intolerance of cardiovascular stress, such as surgeries. Innovative approaches to therapy, such as histone deacetylase inhibitors, and enzyme replacement with cell penetrant peptide fusion proteins, hold promise for this and other similar mitochondrial disorders. This review will focus on the basic findings of this disease, and the cardiomyopathy associated with its diagnosis. © 2011 Elsevier Ireland Ltd.

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