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Tumor necrosis alpha serum levels parallels isolated hypertransaminasemia in the third trimester of pregnancy

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Sir,

Hypertransaminasemia of the 3rd. trimester of pregnancy may be an early finding of some disorders: acute fatty liver (AFLP), haemolysis, elevated liver enzymes, low platelets (HELLP), intrahepatic cholestasis of pregnancy (ICP) and pre-eclampsia.[1] These conditions differ for the frequency (AFLP 1:13000, HELLP 1:1000-6000, ICP 2-7: 1000), clinical course, prognosis and hepatic damage.[2] AFLP is a genetic disorder in the course of an underlying failing in fatty acid oxidation due to mithocondrial trifunctional protein gene defect which results in long chain 3-ketoacyl CoA thiolase (LCHAD) deficiency,[1] whilst recently ICP has been associated to a mutation of a gene codifying for xenobiotic receptors.[3] An increased release of tumour necrosis factor-alpha (TNF-alpha) in HELLP syndrome has been shown thus suggesting that inflammatory mechanisms may participate in the pathophysiology of this disorder.[4] Finally, an isolated hypertransaminasaemia (i. e. a significant elevation of transaminases specifically occurring in the 3rd trimester of pregnancy in the absence of known liver disorders) may be seen in pregnancy. In order to elucidate a possible mechanism sustaining this rare and vague condition, we correlated serum TNF-alpha levels and isolated hypertransaminasemia of the 3rd. trimester of pregnancy in a prospective study.

Nine women at the 3rd. trimester of pregnancy with isolated hypertransaminasemia (Table 1) were recruited in the period January-December 2007 among a sample of 2,160 pregnant women hospitalized in the Obstetrics Unit of our hospital. In these women, TNF-alpha assay was performed using a direct enzyme linked immunosorbent assay kit (Quantikine human TNF-α ELISA kit; R&D Systems Inc. Minneapolis USA) both during pregnancy (group 1) and 3 months after delivery (group 2). Thirty pregnants with normal transaminases were used as control (group 3). Isolated hypertransaminasaemia was confirmed since AFLP was excluded by the absence of specific Glu474Gln mutation detected by real-time polymerase chain reaction in newborn lymphocyte

Table 1. Maternal demographic and clinical characters.

Character	Ist. group	3rd. group
AGE (years)		
• Median age ± SD	27.3 ± 7.5	28.6 ± 6.4
• Range	22-36	22-36
GESTATIONAL AGE (Weeks)		
• Median age ± SD	38 ± 4	38 ± 3
• Range	37-39	37-39
BMI	26.3	25.8
PARITY		
• Primiparity/pluriparity	7/2	21/9

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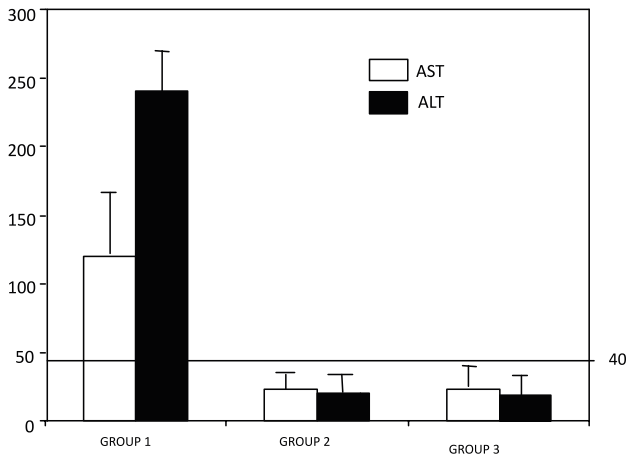

***Figure 1**: Transaminase value comparison in group 1 (pregnant women with isolated hypertransaminasaemia, 2 (same group three months after delivery) and 3 (control group: pregnant women with normal transaminases). Normal value of transaminases was 40 IU/l. Statistical analisys: ANOVA plus Student-neumann-Keuls shows that group 1 > group 2 = group 3.*

DNA after informed consent of parents (Fermentas International INC Canada 830 Harrington Court, Burlington Ontario) and by the administration a standardized questionnaire to the referring paediatricians to investigate the presence of signs/symptoms of LCHAD deficiency at the 1st. year.[5] HELLP was excluded by normal platelet and red blood cell values, ICP by normal bilirubin and bile salts and pre-eclampsia by the absence of hypertension and proteinuria. Finally, negative results were obtained by the exploration of ANAs, HAV-IgM, HBV-DNA, HCV-RNA, minor viruses (cytomegalovirus, Epstein-Barr and Herpes) and alcohol or drug intake history.

Our investigation showed that isolated hypertransaminasaemia prevalence was 0.38% (1: 290), the raise of transaminase values were significantly higher in group 1 when compared to group 2 and 3 ($p < 0.001$). An analogous pattern was observed for TNF-alpha ($p < 0.003$). Spearman's test showed a strong correlation between transaminase and TNF-alpha serum levels only in pregnant women with hypertransaminasaemia (AST: $r = 0.88$, $p < 0.001$; ALT: $r = 0.81$, $p < 0.007$), whilst the correlation was not significant in the control group and three months after pregnancy.

In conclusion, despite hypertransaminasemia of the 3rd. trimester of pregnancy is not a recognized disorder, it represents a finding which likely could be a transient injury of obstetric origin, since it is never been observed in our patients outside the period of pregnancy itself. Our results showed a parallel pattern between serum levels of TNF alpha and transaminases with a simultaneous increase during the 3rd. trimester and a restored normal level after delivery and correlation test confirmed the datum. This, even if obtained in a small number of subjects (the rarity of the condition must be taken into account), suggests a possible involvement of TNF-alpha in liver damage. Since transaminase raise showed a trend to progressively increase, caesarean delivery was performed in order to avoid the possible progression to known pregnancy-related liver disorders, which represent a relevant risk factor for either the mothers and newborns. Therefore, we cannot be sure that isolated hypertransaminasemia could have been the first sign of one the above mentioned disorders. For these reasons, we believe that only multicentre studies on large series of patients may clarify whether our finding is an interesting result or only a speculative assumption.

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