Fetal heart rate acceleration in response to light stimulation as a clinical measure of fetal well-being. A preliminary report

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One of the main problems associated with the management of high-risk pregnancies is the lack of a simple, non-invasive, inexpensive and reliable test for the assessment of fetal condition. For that purpose various tests have been suggested, which are intended to warn the obstetrician of impending fetal demise. While some authors have emphasized the importance of fetal movements in the monitoring of high-risk pregnancy [5], others associated the reaction of fetal heart rate to its movements [2,4].

The purpose of this study is the evaluation of fetal condition in high-risk pregnancies, in which daily fetal movement count is reduced. In those cases we have evaluated the reactivity of the fetal heart rate to a light stimulus.

1 Material and methods

This study consists of 10 high-risk pregnancies with intact membranes, in the 38th to 43rd week of gestation, with fetuses in vertex presentation, in whom the daily fetal movement count was reported to be diminished (as counted by the mothers). An attempt was made to assess the fetal condition in all women, first with the aid of an F.A.D., which failed since difficulties in interpretation of the trace were encountered due to the paucity or absence of fetal movements.

This group included 7 postterm pregnancies and 3 patients with pre-eclamptic toxemia. The fetal heart rate was monitored in these patients by means of external monitoring, with the patient lying flat on her back, in lithotomy position. The tococardiograph used was an H.P. 3028A with ultrasonic stethoscope. The tonus of the uterus was registered in parallel. Following initiation of registration, an amnioscopy was performed in the usual way, while all actions, such as vaginal disinfection, introduction of the amnioscope, etc., were noted on the trace. The amniotic membranes were visualized, so that the amnion and fetus were exposed to cold light for a period of 30 seconds alternatively, while the fetal heart rate and uterine tonus were registered coincidently, and the fetal movements were noted in parallel, as accounted by the parturient. O.C.T.'s were done in all women following the light test. APGAR scores were registered as well in all newborns.

2 Results

In 8 out of 10 cases examined patterns of acceleration of the fetal heart rate reactive to light were obtained. In these fetuses the O.C.T. was negative. APGAR scores of the newborns at 1 and 5 minutes ranged between 8–10. In the 2 other pregnancies non-reactive patterns were registered; in one the O.C.T. was positive; the baby born by Caesarean section showed signs of marked distress, with an APGAR score of 4 following 1 minute and 7 after 5
minutes. In the other case with non-reactive pattern the O.C.T. was negative, and the baby was born in good condition, with Apgar 8 and 10 at 1 and 5 minutes respectively. No meconium was found in the amniotic fluid during amnioscopy in any case.

3 Comment

A reliable test permitting the evaluation of fetal condition in the antenatal period may significantly reduce the perinatal morbidity and mortality. Significant progress in this field has been achieved by the introduction of the non-stress monitoring of the fetus (F.A.D.) [2,4]. This test indeed answers the required conditions; nevertheless, its dependence on the presence of fetal movements precludes its application in many high-risk pregnancies, in which fetal movements are markedly diminished or absent. In fact, the F.A.D. cannot be used in those cases in which one attempts to assess the condition of the fetus in a quiescent period or when it is "asleep". Thus, during monitoring of the hypoactive fetus, it is possible to overcome the problem of absence of movements by provocation of the fetus to move. Other means of such provocation include pressure on the patient's abdomen [6], vibrations [1], as well as sound stimulation [3].

The mechanism of action of the light test seems to be a stimulation of the fetus to move by means of illumination and subsequent reactive acceleration of its heart rate to movements. This hypothesis seems to be confirmed by a lag time between illumination and fetal heart acceleration. In that short period fetal movements are well demonstrated. Acceleration following illumination periods of the amniotic cavity does not appear to be a result of pressure or direct photo-stimulation of reflexory fetal centers for fetal heart acceleration.

In conclusion, this simple test may be done in a relatively large population of women, especially in pregnant women with an inactive or hypoactive
fetus. Further evaluation of the light test in a large number of pregnancies is in order, including those with presenting part other than vertex, with different types of meconium-stained amniotic fluid and various stages of gestation, as well as a wide spectrum of pathological pregnancies.

Summary

Numerous tests have been proposed for the assessment of fetal condition during the antenatal period. This preliminary report suggests the possibility of exposing the fetus-in-utero to alternating light during amnioscopy, with simultaneous registration of the fetal heart rate. This simple, non-invasive, inexpensive test, which may be evaluated instantaneously, shows a good correlation to the condition of the fetus and newborn, as expressed by the O.C.T. and the APGAR score respectively. The advantage of this test is that it is independent of the existence of fetal movements, as well as of the arousal state of the fetus.

Keywords: Light stimulation, nonstress test, O.C.T., reactive/non reactive pattern.
Zusammenfassung

Akzelerationen der fetalen Herzfrequenz nach Lichtreizen als Parameter für die fetale Zustandsdiagnostik – vorläufige Ergebnisse.


Schlüsselwörter: Lichtreize, belastungsfreier Test, Ocytocinbelastungstest, Reaktionsmuster.

Résumé

L’augmentation de la fréquence cardiaque foetale en réponse à la stimulation lumineuse en tant que critère clinique du bien-être foetal’ Rapport préliminaire’

De nombreux test ont été proposés pour apprécier l’état du foetus durant la période anténatale. Ce rapport préliminaire évoque la possibilité d’exposer le foetus in utéro, par amnioscopie, à de la lumière alternative avec enregistrement simultané de la fréquence cardiaque foetale’ Ce test simple, non-invasif et non-expensif que l’on peut apprécier de façon instantanée, montre une bonne corrélation avec l’état du foetus et du nouveau-né, comme le confirment respectivement le test à l’ocytocine et le coefficient d’Apgar. L’avantage de ce test réside en son indépendance des mouvements foetaux, aussi bien que du l’état d’éveil du foetus.

Mots-clés: Modele reactif/non-reactif, non-stress test, P.O., stimulation lumineuse.

Bibliography


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The genetic component of quantitative perinatal variables. An analysis of relations between erythrocyte acid phosphatase phenotype and birth weight, gestational age and serum bilirubin level in the first days of life


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1 Introduction

Both genetic and environmental factors influence intrauterine development. However, since the hygienic and nutritional conditions in human populations are continually improving, increasing importance is being given to the genetic factors affecting development and feto-neonatal morbidity. The studies on the identification of specific genetic factors influencing intrauterine development have till now mainly concerned monofactorial diseases, chromosomal aberrations and feto-maternal incompatibility. These conditions are generally scarcely dependent on environmental factors and the relevant biological characteristic shows a bimodal distribution with a distinct separation between "normal" and "pathological".

In many pathological situations a polygenic inheritance is presumed. In these conditions environmental factors are of great importance. The relevant biological characteristic is presumed to be normally distributed with a threshold value beyond which there is a definite risk of disease. The identification of specific genetic factors which influence multifactorial diseases is of both theoretical and practical importance, especially in disease prevention. Research in this area should be directed towards the identification of those factors which determine "normal variability". Genetic polymorphisms are therefore the most important candidates for this type of analysis [1, 7].

For several years our research group has studied erythrocyte acid phosphatase polymorphism (ACP), especially in relation to hemolytic conditions. Erythrocyte acid phosphatase is a SH dependent enzyme which shows an electrophoretic polymorphism determined in Caucasian populations, by the occurrence of three common alleles (P\textsuperscript{A}, P\textsuperscript{B} and P\textsuperscript{C}) at an autosomal locus. Correspondingly six electrophoretic phenotypes are observed: A, B, C, BA, CA and CB. The six phenotypes show decreasing enzymatic activity in the following order C > CB > CA > B > BA > A. C phenotype is very rare [8,9,10].

In order to determine the selective forces acting on this system and to investigate its physiological and pathological role, we considered of great importance the fact that erythrocyte acid phosphatase is an SH dependent enzyme particularly susceptible to oxidized glutatione (GSSG) [4,5, 11]. From this point of view, those situations in which damage to the SH dependent structures presumably play a central pathogenetic role (oxydative hemolysis) are of particular interest.

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Hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency is an example of this type of condition. A transient condition, common to all human populations, is the erythrocyte's greater vulnerability to oxidative damage observed during the neonatal period. It is well known that the critical factor in the development of "physiological" jaundice is the inability of the newborn liver to adapt itself to the extrauterine environment and to readily handle the total bilirubin load. Nevertheless attention should also be focused on mechanisms responsible for the increased hemoglobin catabolism since the impairment of hepatic clearance of the newborn may exaggerate the effects of even small increases of bilirubin production.

In this paper the relation between ACP<sub>1</sub> polymorphism and some quantitative neonatal variables, which are probably multifactorial, was investigated. The neonatal variables considered were birth weight, gestational age and bilirubin levels in the first few days of life. A partial preliminary report concerning some data on serum bilirubin levels has been already published as a letter to the Editor [6].

2 Material and methods

Two consecutive series of newborn babies were studied in the Neonatal Section of the Dept. of Child Health of Rome University. In the first series of 229 infants total serum bilirubin levels from birth (cord sample) to the fifth day of life, every 24 hours, were determined by means of OHC-photometer. ACP<sub>1</sub> phenotype was determined at birth by starch gel electrophoresis [8,9]. Sex, birth weight, gestational age, ABO and Rh feto-maternal compatibility were recorded. In the second series of 189 infants only ACP<sub>1</sub> phenotype was determined. Sex, birth weight and gestational age were also recorded.

3 Results

In Tab. I the distributions of birth weight, gestational age, ABO and Rh feto-maternal compatibility and ACP<sub>1</sub> phenotypes in the first series of infants are reported. Treated (by phototherapy or by exchange-transfusion) and untreated subjects are also tabulated. The proportions of the four classes of compatibility are very close to those expected on the basis of ABO and Rh gene frequencies.

Tab. II shows the mean values and standard deviations of mean and maximum bilirubin level (calculated during the first 5 days of life) and of its increment in the first 24 hours of life for the five acid phosphatase phenotypes. F values and corresponding probability values for analysis of variance are also reported. The highest mean values of the three bilirubin parameters are observed in subjects showing CA phenotype. The values of F statistic for analysis of variance show

| Tab. I. Sample distribution of some relevant variables in the first series of 229 infants. Treated (by phototherapy or by exchange-transfusion) and untreated subjects are tabulated separately. |
|-----------------|-------------|-------------|
|                  | Total       | Treated     | Untreated   |
| Birth weight (gr)|             |             |             |
| < 2500          | 14          | 5           | 9           |
| > 2500          | 215         | 19          | 196         |
| Gestational age (days) |             |             |             |
| < 259           | 17          | 5           | 12          |
| 259 ± 293       | 199         | 17          | 182         |
| > 294           | 13          | 2           | 11          |
| ABO and Rh feto-maternal compatibility |             |             |             |
| ABO and Rh compatible | 163        | 17          | 146         |
| Rh incompat.    | 21          | 4           | 17          |
| ABO incompat.   | 39          | 3           | 36          |
| ABO and Rh incompatible | 6          | 0           | 6           |
| A               | 19          | 2           | 17          |
| B               | 112         | 12          | 100         |
| BA              | 78          | 7           | 71          |
| CB              | 13          | 1           | 12          |
| CA              | 7           | 2           | 5           |

Tab. II. Mean values and standard deviations of mean and maximum serum bilirubin levels during the first five days of life and of increment of serum bilirubin level during the first 24 hours of life calculated for the five acid phosphatase phenotypes in the first series of 229 infants.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Mean bilirubin</th>
<th>Maximum bilirubin</th>
<th>Bilirubin increase in the first 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.2 ± 1.3</td>
<td>7.6 ± 2.4</td>
<td>3.2 ± 1.3</td>
</tr>
<tr>
<td>B</td>
<td>5.1 ± 1.7</td>
<td>7.7 ± 3.1</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td>BA</td>
<td>5.1 ± 1.6</td>
<td>8.0 ± 2.8</td>
<td>3.1 ± 1.8</td>
</tr>
<tr>
<td>CB</td>
<td>4.5 ± 2.1</td>
<td>6.8 ± 3.6</td>
<td>3.0 ± 1.4</td>
</tr>
<tr>
<td>CA</td>
<td>6.5 ± 1.6</td>
<td>9.6 ± 2.7</td>
<td>4.2 ± 0.9</td>
</tr>
<tr>
<td>All phenotypes</td>
<td>5.1</td>
<td>7.8</td>
<td>3.2</td>
</tr>
<tr>
<td>F</td>
<td>3.7</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>p</td>
<td>0.05</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

that the differences between CA and the other phenotypes is significant for mean bilirubin level. Tab. III shows the mean values of bilirubin variables for the five acid phosphatase phenotypes, F and probability values for analysis of variance calculated separately for males and females. Significantly higher mean bilirubin values are observed in females of CA phenotype only.

Twenty-one babies were treated by phototherapy and three by exchange transfusion. Tab. IV shows the mean value of mean serum bilirubin levels in the "treated" and "not treated" groups. The frequency of CA phenotype is higher in "treated" infants than in those "not treated". Serum bilirubin levels in "not treated" infants is higher in CA phenotypes than in other ACP₁ phenotypes.

Tab. V shows the distribution of ACP₁ phenotypes in both series of infants. No significant difference is observed between males and females.

Mean values and standard deviations of birth weight and gestational age for CA and other ACP₁ phenotypes are reported in Tab. VI, it values and corresponding probability values for differences between means are also shown. Birth weight and gestational age of CA infants appear lower than those of other ACP₁ phenotypes. The differences are significant in male infants only.

4 Discussion

Our group has already shown that CA phenotype subjects with G-6-PD deficit have a higher susceptibility to favism [2]. Moreover a retrospective study carried out on a series of subjects admitted to Hospital in the first few days of life for jaun-

Tab. IV. Mean serum bilirubin levels (mg/dl) in treated (by phototerapy or exchange-transfusion) and untreated subjects of the first series of 229 infants.

<table>
<thead>
<tr>
<th>ACP₁ phenotype</th>
<th>Treated</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>N° 24</td>
<td>205</td>
</tr>
<tr>
<td>mean value</td>
<td>7.48</td>
<td>4.86</td>
</tr>
<tr>
<td>S.D.</td>
<td>1.03</td>
<td>1.56</td>
</tr>
<tr>
<td>CA</td>
<td>N° 2</td>
<td>5</td>
</tr>
<tr>
<td>mean value</td>
<td>7.55</td>
<td>5.90</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.15</td>
<td>1.75</td>
</tr>
<tr>
<td>Others</td>
<td>N° 22</td>
<td>200</td>
</tr>
<tr>
<td>mean value</td>
<td>7.47</td>
<td>4.84</td>
</tr>
<tr>
<td>S.D.</td>
<td>1.08</td>
<td>1.55</td>
</tr>
</tbody>
</table>

Tab. V. Distribution of erythrocyte acid phosphatase phenotypes in both series of infants

<table>
<thead>
<tr>
<th>ACP₁ phenotype</th>
<th>All infants</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>36 (8.6)</td>
<td>18 (8.4)</td>
<td>18 (8.3)</td>
</tr>
<tr>
<td>B</td>
<td>211 (50.5)</td>
<td>103 (48.1)</td>
<td>108 (52.9)</td>
</tr>
<tr>
<td>BA</td>
<td>126 (30.1)</td>
<td>68 (31.8)</td>
<td>58 (28.4)</td>
</tr>
<tr>
<td>CB</td>
<td>32 (7.7)</td>
<td>20 (9.3)</td>
<td>12 (5.9)</td>
</tr>
<tr>
<td>CA</td>
<td>13 (3.1)</td>
<td>5 (2.3)</td>
<td>8 (3.9)</td>
</tr>
</tbody>
</table>

dice, showed a proportion of CA phenotypes significantly higher than in the control population [3].

On the basis of the previous observations and of the results given in this paper the existence of a relation between CA phenotype and higher bilirubin levels in neonatal period can be considered reasonably established. In fact both a retrospective and a prospective series of data have shown similar results.

Recent evidence indicates that ACP1 acts in vivo as a flavin-mono-nucleotide phosphatase. It has also been shown that ACP1 is inhibited by folic acid and by various folates, the phenotype dependence of inhibition being in the order B < BA < A < CB < CA < C [12]. The greater risk of hemolysis associated with the presence of Pa and Pb fits the pattern predicted by folate inhibition effect [12].

It appears suggestive that also the relation between intrauterine development and ACP1 phenotype fits the same pattern. However, since the number of CA phenotypes is still rather small, this relation should be confirmed by further research.

It is well known that low birth weight is associated with higher bilirubin levels. Thus the relation between CA phenotype and hyperbilirubinemia could be dependent on the relation between this genetic factor and birth weight. However, the striking differences observed between sexes seem to suggest that the relation between bilirubin levels and acid phosphatase phenotype is not dependent on that between ACP1 and gestational age and/or birth weight.

## Summary

The investigations on the identification of specific genetic factors influencing intrauterine development have till now mainly concerned monofactorial diseases, chromosomal aberrations and fetomaternal incompatibility. In many pathological situations a polygenic inheritance is presumed. In these conditions environmental factors are of great importance. The relevant biological characteristic is presumed to be normally distributed with a threshold value beyond which there is a definite risk of disease. The identification of specific genetic factors which influence multifactorial diseases is of both theoretical and practical importance, especially in disease prevention. Research in this area should be directed towards the identification of those factors which determine "normal variability". Genetic polymorphisms are therefore the most important candidates for this type of analysis.

For several years our research group has studied erythrocyte acid phosphatase polymorphism (ACP1), especially in relation to hemolytic conditions. In this paper the relation between ACP1 polymorphism and some quantitative neonatal variables, which are probably multifactorial, was studied. The neonatal variables considered were serum bilirubin levels in the first few days of life, birth weight and gestational age.

Two consecutive series of newborn infants (229 and 189 subjects respectively) were studied in the Neonatal Section of the Dept. of Child Health of Rome University. Tab. II shows the mean values and standard deviations of mean and maximum bilirubin level (in the first 5 days of life in the series of 229 newborn babies) and of its increment during the first 24 hours of life for the five acid phosphatase phenotypes. The highest mean values of the three bilirubin parameters are observed in subjects showing CA phenotype.

Tab. VI shows the mean values and standard deviations of birth weight and gestational age calculated for CA and other ACP1 phenotypes in both series (n° 418) of infants. Birth weight and gestational age of CA infants appear lower than that of other ACP1 phenotypes.

Our group had already shown that CA phenotype subjects with G-6-PD deficit have a higher susceptibility to favism. Moreover a retrospective study carried out on a series of infants admitted to Hospital during the first few days of life for jaundice, had also shown a proportion of
CA phenotype significantly higher than in the control population. On the basis of the previous observations and of the results given in this paper the existence of a relation between CA phenotype and higher bilirubin levels in the neonatal period can be considered reasonably established.

**Zusammenfassung**


**Schlüsselwörter:** Genetischer Polymorphismus, intrauterine Entwicklung, Krankheitsprävention, Serumbilirubinspiegel.

**Résumé**

La composante génétique des variables périnatologiques quantitatives. Une analyse des relations entre le phénotype de la phosphatase acide érythrocytaire et le poids de naissance, la durée de la grossesse et les taux de bilirubine sérique au cours des premiers jours de la vie.

Les recherches sur l'identification de facteur génétiques spécifiques influençant le développement intrautérin ont porté jusqu'à présent principalement sur les affections monofactorielles, les aberrations chromosomiques et l'incompatibilité foeto-maternelle. L'on suppose une
hérité polygénétique dans plusieurs états pathologiques. Sous cet aspect, des facteurs d’environnement prennent une grande importance. L’on peut admettre que la caractéristique biologique principale se distribue normalement et qu’avec le franchissement d’un certain seuil un état pathologique survient avec une probabilité définie. L’identification de facteurs génétiques spécifiques conditionnant des maladies multifactorielles est à la fois d’importance théorique et pratique, en particulier dans la prévention de l'affection. La recherche dans ce domaine devrait donc être dirigée vers l’identification de ces facteurs qui déterminent «la variabilité normale». Les polymorphismes génétiques sont ici les candidats les plus importants pour ce type d’analyse.

Pendant plusieurs années notre groupe de recherches a étudié le polymorphisme de la phosphatase acide érythrocytaire (ACP), particulièrement en relation avec des conditions d’hémolyse. L’objet de ce travail a été l’étude de la relation entre le polymorphisme ACP et quelques variables néonatologiques quantitatives, probablement multifactorielles. Les variables néonatologiques prises en considération étaient les taux de bilirubine sérique au cours des premiers jours de vie, le poids de naissance et la durée de grossesse.

Deux séries consécutives de nouveaux-nés (respectivement de 229 et 189 enfants) ont été étudiées dans la Section de Néonatologie du Département de Pédiatrie de l’Université de Rome.

La fig. 2 montre les valeurs moyennes et les déviations standart des taux moyen et maximum de bilirubine (au cours des 5 premiers jours de vie dans la série de 229 nouveaux-nés) ainsi que leur augmentation pendant les 24 premières heures de vie pour les 5 phénotypes de phosphatase acide. Les moyennes les plus élevées des trois paramètres de bilirubine ont été relevées chez les sujets présentant le phénotype CA.

Le tableau 6 montre les valeurs moyennes et les déviations standart des poids de naissance et des âges gestationnels calculés pour le CA et autre ACP- phénotype dans les deux séries d’enfants (n=418). Le poids de naissance et l’âge gestationnel des enfants CA apparut inférieur à celui des autres phénotypes ACP.

Notre groupe a déjà montré que les sujets du phénotype CA avec un déficit de G-6-PD sont d’avantage susceptibles de favisme. D’autre part une étude rétrospective sur une série d’enfants admis au Service au cours des premiers jours de vie pour ictere a montré une proportion de phénotype CA nettement plus élevée que dans la population de contrôle.

A la suite des observations précédentes et des résultats présentés dans cet article on peut raisonnablement admettre la relation entre le phénotype CA et l’hyperbilirubinémie néonatale. En effet, les deux series de données, retrospective et prospective, ont abouti à des résultats similaires. Cependant, vu le nombre réduit de phénotypes CA il semble nécessaire de confirmer par des recherches ultérieures la relation entre le phénotype de la phosphatase acide et le poids de naissance ainsi que la durée de grossesse.

Mots-clés: Bilirubinémie sérique, développement intrautérin, polymorphisme génétique, prévention des maladies.

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