Some Physiological Changes in Infantile Hyperbilirubinimia

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Abstract:

This study was designed to estimate some hematological and biochemical changes in hyperbilirubinic patients .The levels of these substances are very important in letting the health care team to know how the body is responding to the different therapies that being provided and this will help the medical staff for proper management .

The study lasted from Desember/2009 to Jaune/2010. The patients are 106 with neonatal jaundice (65 males 41 females), and 84 controls are taken in this study (clinically assessed by specialist) .The patients (1day- <30days) are classified into 4 subgroups: The first subgroup(A):- The blood group is similar between the mother and baby, The second subgroup(B):- the blood group is different between the mother and baby, The third subgroup(C):- the (RH) differences between the mother and baby and The fourth subgroup (D):- have G6PD deficiency.

Those patients were admitted to the Babylon maternity and children teaching hospital .Concerning the hematological parameters, it is found that the hemoglobin (Hb) and packed cell volume (PCV) showed significant decrease ($p<0.05$) in subgroup C&D in comparison with controls. The white blood cells (WBCs) count showed no significant changes (p values>0.05) in comparison with controls (except the subgroup D) which showed significant increase in comparison with controls. The red blood cells count RBCs count showed no significant changes (p values>0.05) in all subgroups in comparison with controls. Regarding the biochemical parameters, the serum of total and indirect bilirubin showed significant increase ($p <0.05$) for all sub groups in comparison with controls. Regarding the serum Zinc and GSH which showed significant decrease of all values in comparison with controls , while the serum Copper showed significant increase for males and females of all age groups in comparison with controls, except the subgroup A which showed no significant changes in comparison with controls.

الخلاصة:

تضمنت هذه الدراسة معرفة التغييرات التي تحدث لبعض المعايير الدموية والكيميوحيوية لدى مرضى اليرقان وذلك لأهميتها في مساعدة الفريق الطبي لمعرفة كيفية استجابة الجسم للعلاج المعطى مؤدياً إلى علاج أفضل .

شملت الدراسة(١٠٦) طفل منهم (٦٥ ذكور و ٤١ إناث) مصابين باليرقان الولادي أدخلوا إلى ردهة الأطفال في مستشفى بابل للنسائية و الأطفال خلال فترة ستة أشهر بين كانون الثاني إلى حزيران لسنة ٢٠١٠ .

الأطفال المصابين باليرقان قسموا إلى أربع فئات : الفئة الأولى تضمنت تشابه فصائل الدم بين الأم والطفل ، الفئة الثانية فتشتمل اختلاف فصائل الدم بين إلام والطفل ، الفئة الثالثة تحتوي على اختلاف عامل (RH) الريس،إما الفئة الرابعة فقد شملت الأطفال المصابين بمرض عوز نازعة هيدروجين الكلوكوز-٦- فوسفاتة. العينة الضابطة التي تم المقارنة بها اشتملت على ٨٤ طفلاً من اللذين تم إدخالهم إلى شعبة الخدج والطوارئ لأسباب أخرى غير اليرقان .لكل الأطفال تم أخذ التاريخ المرضي للطفل وتم إجراء فحص سريري كامل كما خضع الأطفال لفحوص مختبرية اشتملت على صنف الدم والعامل الرئيسي ،مسّحة كاملة للدم مع بيان عدد كريات الدم الحمر غير الناضجة،وفحص متكرر لنسبة المادة الصفراء في الدم.تميز الأشخاص المصابين باليرقان فيما يخص الوزن في الفئة العمرية (A)إناث وكل من الفئة العمرية(B)و(C)و(D) في المجموعة الأولى وكل من الفئتين في المجموعة الثانية بانخفاض معنوي ($p <0.01$)عند المقارنة بالأصحاء. فيما يخص المتغيرات الدموية بانخفاض معنوي ($p <0.01$) لكل من خضاب الدم (Hb) وحجم الخلايا المضغوط (PCV) لكل المجاميع العمرية ومن كلا الجنسين عند مقارنتها بالأصحاء عدا الفئتين الأولى والثانية ، والثانية)،إما بالنسبة للعدد الكلي لخلايا الدم البيضاء(WBCs) فقد وجد لوحظ ارتفاعا معنويا في مصل الدم عند مقارنتها بالأصحاء في كل من الفئة الرابعة ومن كلا الجنسين . ،كما لوحظ عدم وجود تغيير معنوي ($p < 0.01$) في كل من العدد الكلي لخلايا الدم الحمر (RBCs) ،

وأما بخصوص المتغيرات الكيميوحيوية فقد لوحظ في معدل البلروبين الكلي والغير مباشر (total& indirect bilirubin) ارتفاعا معنويا في مصل الدم في كل الفئات ومن كلا الجنسين عند مقارنتها بالأصحاء وإما البلروبين المباشر (direct bilirubin) فقد لوحظ عدم وجود تغيير معنوي عند مقارنتها بالأصحاء .كما شهد كل من العنصر النادر (الزنك) و الكلوتاثيون انخفاضاً معنوياً($p<0.05$) في كل المجاميع العمرية ومن كلا الجنسين،إما العنصر النادر(النحاس) فقد شهد ارتفاعا معنويا في مصل الدم عند مقارنتها بالأصحاء (عدا كل من الفئة الأولى من كلا الجنسين) فقد وجد عدم وجود تغيير معنوي عند مقارنتها بالأصحاء.

Introduction

Jaundice is defined as a yellow discoloration of the skin, sclera and mucous membranes caused by hyperbilirubinemia, and it is also known as ictrus (22). The concentration of bilirubin in the blood must exceed 2-3mg/dl for the color to be visible. It is may be associated with Glucose-6- Phosphate Dehydrogenase (G6PD) Deficiency (1,9&18). Poor caloric intake and/or dehydration associated with inadequate breastfeeding subsequent weight loss, delayed passage of stool, and bruising from delivery place the infant at high risk for jaundice (9,16&19).

The Aim of the study

This study aims to estimate some hematological and biochemical changes in jaundiced neonates, and G6PD deficit infants attending the Babylon maternity and children teaching hospital. So this study is designed to determine the following:-

1. The hematological study which includes :-

- Total RBCs count, PCV, and total WBCs count.
- To identify the frequency of G6PD deficiency in neonatal jaundice.

2. The biochemical study which includes:-

- TSB, direct and indirect bilirubin, the level of (GSH) concentration as non- enzymatic antioxidant in serum, and the serum of Zinc and Copper.
- To determine the frequency of hyperbilirinimia in male and female.

Neonatal Jaundice

Bilirubin is formed from the breakdown of hemoglobin in red blood cells. Red blood cells (RBCs) only live for 70-90 days in the newborn period, unlike the older child whose cells live 120 days (5). In addition, incidence of acute bilirubin encephalopathy (Kernicterus) has increased among otherwise healthy breastfed infants with poor feeding and delayed follow up visits (1). Kernicterus is may be associated with Glucose 6Phosohate Dehydrogenase Deficiency G6PDd (1&18).Newborns are breastfed are three times more likely to have total bilirubin levels >12 mg/dl than bottle-fed infants as there may be considerable delay before breastfeeding is well established (2).

Differentiation between physiological and pathological jaundice (5)

Physiological

1: Visible at 2-3 days of birth and mostly at 4-6 days after birth.
2: Absent after 2, 3-4weeks.
3: For full term and preterm infant TSB<12mg/dl, <15mg/dl respectively.
4: No disorders were found.

Pathological

1: Clinical jaundice in first 24 hr of life.
2: Total serum bilirubin >12-15mg/dl or increase by 5 mg/dl a day.
3: Direct serum bilirubin>1.5-2mg/dl.
4: Prolonged jaundice.
5: Recurrence of jaundice. (15).

Causes of indirect hyperbilirubinemia:- (15).

A: Hemolysis disorders:-
1. feto-maternal blood incompatibility.
2. Genetic causes of hemolysis.
a: Hereditary spherocytosis.
b: Enzymatic defect (G6PD), pyruvate kinase deficiency.
c: Haemoglobinopathy (thalassemia).
d: Galactosemia.
3: Drug induced haemolysis (vitamin k).
B: Extra vascular blood (petechie), hematoma, pulmonary and cerebral hemorrhage, swallowed blood.
C: Polycythemia:-
1. Chronic fetal hypoxia.

2. Materno-fetal or feto-fetal transfusions.
3. Placental transfusions (cord striping).
D: Exaggerated entero hepatic circulation:-
1. Mechanical obstruction.
a-atresia and stenosis.
b- hurschprung disease.
c- meconium illus.
d- meconium plug syndrome.
2. Reduced perstalisis.
a- fasting.
b- Drugs.
c- Pyloric stenosis.
E: Reduced hepatic uptake of bilirubin:-
Persistence of ductusc venosus shunt.
F: Decreased bilirubin conjugation :-
1. Congenital reducto glucourenyl transferase.
a- familial non hemolytic jaundice.
b- Gilbert disease.
2. Enzyme inhibitor galactosemia.

Types of Neonatal Jaundice:-

From a management perspective, it is useful to categorize severe hyperbilirubinemia according to its time of onset, early or late, regardless of its specific etiology (Table 1) (13).

Table: (1) Differential diagnosis of neonatal hyperbilirubinemia based on pathophysiology(8).

<table>
<tr><td colspan="2">Early onset hyperbilirubinemia
(age <72 h)</td><td colspan="2">Late onset hyperbilirubinemia
(age >72h <2 weeks)</td></tr>
<tr><td>First 24 hours of life</td><td>First week of life</td><td colspan="2">> 1 week of life</td></tr>
<tr><td rowspan="3">Direct Coombs positive isoimmune erythroblastosis fetalis:
• rhesus disease
• minor blood group incompatibilities.
• ABO (often the direct Coombs is negative).</td><td>Benign idiopathic Jaundicephysiologic;<40th percentile)</td><td colspan="2">Prolonged idiopathic jaundice (breast milk jaundice; TSB< 13mg/dl)</td></tr>
<tr><td>Sepsis (viral or bacterial).</td><td colspan="2">Sepsis (viral or bacterial).</td></tr>
<tr><td>Increased enterohepatic circulation.</td><td colspan="2">Functional gastrointestinal tract abnormality.</td></tr>
<tr><td rowspan="3">Direct Coombs negative:
• G6PD deficiency.
• Intrinsic red blood cell defect.
• Spherocytosis.
• Elliplocytosis.
• Hemoglobinopathies.</td><td colspan="3">Disorders of bilirubin metabolism:
• UGITAI gene polymorophisms (delayed coajugation)
• Co-inherithance of UGITAL polymorphism with G6PD deficiciency, ABO incompatibility& Spherocytosis.
• Crigler-Naajar syndromes: I and II.
• Gilbert syndromes.
• Others.
Metabolic disorders:
• galactosemia .
• alpha-1-antitrypsin deficiency.
• storage diseases.
• others.</td></tr>
<tr><td>Enclosed hemorrhages:
• cephalhmatoma, subaponeurotic hemorrhage.
• Bruising.</td><td>• Cystic fibrosis .
• Hypothyrodism .</td></tr>
</table>

Early- onset hyperbilirubinemia (TSB values >75th percentile prior to 72 h of age or >13 mg/dl) is a high-risk condition because it often presents with an acute and rapid rise in TSB values, which might reach levels above the 95th percentile (> 17 mg/dl) within the first 12 h of life (8).

Late-onset hyperbilirubinemia(TSB values > 95th percentile after 72 h of age)can usually be predicted by predischarge bilirubin screening.

Severe hyperbilirubinemia with a TSB >25 mg/dl is associated with an increased risk for bilirubin – induced neurologic dysfunction (BIND) , which occurs when bilirubin crosses the blood-brain barrier and binds to brain tissue. The case definition for severe hyperbilirubinemia is a neonate with total serum bilirubin concentration of more than 20 mg\dl in the first month of life (14).

Risk Factors for Hyperbilirubinemia:-

- Infants without identified risk factors rarely have total serum bilirubin levels above 12 mg per dl. As the number of risk factors increases, the potential to develop markedly elevated bilirubin levels also increases (10).

Major risk factors:- (1).

- TSB / Transcutauosbilirubin level at discharge in the high-risk zone.
- Jaundice observed in the first 24 hr.
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (G6PD deficiency).
- Gestational age 35-36 WKs.
- Previous sibling received phototherapy.
- Cephalohematoma or significant bruising.
- Delay breast feeding, particularly if nursing is not going well and weight loss is excessive.
- East Asian race.

Minor risk factors:- (1).

- TSB / Transcutauosbilirubin level at discharge in the high Intermediate-risk zone.
- Gestational age 37-38 WK
- Jaundice observed with discharge.
- Previous sibling with jaundice.
- Macrosomic infant of a diabetic mother.
- Maternal age > 25 yr.
- Male gender.

Factors decreased risk of development severe hyperbilirubinemia:- (16)**.**

- TSB /Transcutauosbilirubin level at discharge in the high low-risk zone.
- Gestational age >41 WK.
- Black race.
- Discharge from hospital after 72 hr**.**

Table.A : The mean and stander error(SE) of age and weight (Wt) in male and female with neonatal jaundice.

Age (1day-<30day)	Sex	Age		Wt/Kgm	
		Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)
SUBGROUP A (similar blood group between mother &neonate)	M	8.416±1.154	8.285± 1.322	3.025± 0.165	3.742 ± 0.169
	F	8 ± 0.522	8± 0.8165	* 2.591± 0.222	3.957 ± 0.125
SUBGRUOP B Different blood group between mother &neonate)	M	6.393± 0.405	6.571±0.895	* 2.972 ±0.126	3.55 ± 0.131
	F	6.235 ± 0.661	6.142 ± 0.799	* 2.441 ±0.181	3.742 ± 0.141
SUBGROUP C (Rh incompatibility)	M	7.5 ± 1.176	7.571±1.461	* 3.358 ± 0.244	4.085± 0.171
	F	7.3±0.817	7.571±1.461	** 3.345 ± 0.152	4.085 ± 0.171
SUBGROUP D (G6PDd neonate)	M	6.571± 3.183	6.571± 0.895	* 2.364 ± 0.461	3.55± 0.131
	F	6.166± 1.424	6.571 ±0.895	* 2.483 ± 0.29	3.55± 0.131

-Means without * are insignificant P value > 0.05.

Table B: The mean and stander error (SE)oftotal white blood cells(WBCs) count, red blood cells (RBCs) count, packed cell volume(PCV) and hemoglobin in male(M) and female (F) with neonatal jaundice .

Age (1day-<30day)	Sex	WBC 10^3/mm		RBCs count millions/mm^3		PCV L/L		Hb g/dl	
		Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)
SUBGROUP A (similar blood group between mother&neonate)	M	6.979 ± 0.605	6.928± 0.276	4.492± 0.09	4.524±0.277	0.494± 0.019	0.49±0.018	15.46 ± 0.645	15.31 ± 0.61
	F	6.375 ± 0.647	6.428 ± 0.399	4.452± 0.073	4.347± 0.104	0.497 ±0 .036	0.495±0.023	15.716 ± 0.875	15.314 ± 0.737
SUBGRUOP B Different blood group between mother &neonate)	M	6.075 ± 0.424	6.742 ± 0.369	4.860 ± 0.1	4.325 ± 0.09	0.493±0.012	0.492±0.022	15.786 ±0.430	15.1± 0.788
	F	6.241 ± 0.546	6.142 ± 0.508	4.274 ± 0.045	4.242 ±0.061	0.492 ±0.024	0.492±0.026	15.370 ±0.794	15.257 ±0.886
SUBGROUP C (Rh incompatibility)	M	7.616± 1.62	7.171 ± 0.392	4.981± 0.294	4.335 ± 0.044	* 0.413 ± 0.036	0.49±0.034	** 13.8 ±1.186	17.3 ±1.12
	F	7.81 ± 0.383	7.171 ± 0.392	4.28 ± 0.131	4.135 ± 0.044	** 0.405±0 .02	0.528±0.034	* 13.22± 0.691	17.3 ±1.12
SUBGROUP D (G6PDd neonate)	M	** 14.157 ± 1.092	6.742 ± 0.369	4.398 ± 0.133	4.325 ± 0.09	* 0.344± 0.023	0.482±0.022	* 11.118 ±0.788	15.75± 0.766
	F	* 12.08 ± 1.579	6.74± 0.37	4.501 ± 0.265	4.425± 0.09	** 0.38± 0.026	0.482 ±0.022	* 12.393 ± 0.923	15.75± 0.766

- * (p < 0.05).
- ** (p < 0.01).
-Means without * are insignificant P value > 0.05.

TableC : The mean and stander error (SE) of total serum bilirubin (TSB) ,direct and indirect serum bilirubin in male and female with neonatal jaundice.

Age (1day-<30day)	Sex	TSB mg/dl		Direct serum bilirubin mg/dl		Indirect serum bilirubin mg/dl	
		Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)
SUBGROUP A (similar blood group between mother&neonate)	M	* 13.158± 0.597	1.928 ± 0.086	0.44 ±0 .01	0.24 ± 0.02	* 12.67± 0.591	1.7± 0.09
	F	* 14.066 ± 0.685	2.171± 0.071	0.5± 0.348	0.3± 0.03	** 13.816 ± 0.637	1.871 ± 0.068
SUBGRUOP B (different blood group between mother &neonate)	M	* 14.651± 0.597	4.342 ± 0.289	0.54 ±0.026	0.457 ± 0.02	* 13.959 ± 0.698	3.885 ±0.297
	F	** 12.982 ± 0.623	3.757 ± 0.085	0.535 ±0.02	0.4 ± 0.03	* 12.447 ± 0.61	3.357 ± 0.436
SUBGROUP C (Rh incompatibility)	M	* 12.966 ± 0.978	2.214± 2.562	0.483 ± 0.04	0.371 ±0.042	* 12.483± 0.956	1.842 ±0.089
	F	* 17.78 ± 1.722	1.857 ±0.142	0.57 ± 0.036	0.371 ± 0.042	** 17.21 ± 1.702	1.842 ± 0.08
SUBGROUP D (G6PDd neonate)	M	* 15.957± 2.212	3.342±0.289	0.442 ±0.042	0.442± 0.029	* 15.514 ± 2.181	3.928 ± 0.29
	F	** 15.083± 1.3	3.342 ±0..89	0.466 ± 0.021	0.442± 0.029	* 14.616 ± 1.294	3.928 ± 0.29

- * (p < 0.05).
- ** (p < 0.01).
-Means without * are insignificant P value > 0.05 .

Table D : The mean and stander error (SE) of Serum glutathione (s.GSH), serum copper (s.Cu)and serum zinc(s.Zn) in male and female with neonatal jaundice.

Age (1day-<30day)	SEX	S.GSH µmol/l		S.CU µg/dl		S. Zn ug/dl	
		Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)	Patients (mean ± SE)	Controls (mean± SE)
SUBGROUP A (similar blood group between mother&neonate)	M	4.88 ± 0.66 *	7.95 ± 1.16	38.54 ± 4.857	38.142±3.019	74.716± 2.133 **	77.571± 1.428
	F	4.82 ± 0.61 *	7.89± 1.15	37.807 ± 5.7	37.428± 0.751	62.047± 5.77 **	75.428± 1.36
SUBGRUOP B (different blood group between mother &neonate)	M	4.78 ± 0.59 *	7.91 ±1.14	37.833 ± 4.23 *	27.885± 6.040	60.50±2.971 *	72.857±1.01
	F	6.74 ± 0.52	7.89 ±1.12	37.852 ± 5.521	34.714± 2.997	64.805± 3.2	76.857±1.28
SUBGROUP C (Rh incompatibility)	M	4.66 ± 0.51 *	7.92 ± 1.14	48.416 ± 12.018 *	32.857±2.971	72.833± 2.495 *	83.142± 1.765
	F	4.59 ± 0.50	7.88 ± 1.4	73.85 ± 5.219	32.857± 2.971	68.08± 5.922 **	83.142± 1.765
SUBGROUP D (G6PDd neonate)	M	4.49 ± 0.71 *	7.91 ± 1.13	86.714 ± 4.586 *	71.885±6.04	56.6±4.329 **	72.857±1.01
	F	4.41 ± 0.069	7.85 ± 1.1	45.333 ± 0.614	71.885 ± 6.04	18.666± 0.494 *	72.857± 1.01

- * (p < 0.05).
- ** (p < 0.01).
-Means without * are insignificant P value > 0.05 .

Discussion

History

There was a significant difference in weight of subgroup A female and subgroup B, C and D with neonatal jaundice in comparison with controls, while there was no significant difference in weight of subgroup A male subgroup B G6PD deficit patients and controls (table A). There was a low birth weight in newborns with hyperbilirubinemia especially in G6PD deficient neonates. Similar cases to study in UK and Ireland, which showed 60.4% of cases with severe jaundice were males (7).

Hematological Studies :

WBCs count

There was no significant difference of WBCs count in subgroup A, B and C but there was significant difference between subgroup D and control (tableB). These results agreed with (2) and (4), who suggest a significant hemolysis due to G6PD deficiency because G6PD enzyme plays an important role in protecting RBCs and Hb from oxidative stress.

RBCs count

The values of RBCs count and indices for all subgroups of males and females are insignificantly decreased in comparison with controls,(table B).These results agreed with (11) who stated that G6PD deficient neonate was confirmed the presence of hemolysis.

Hb and PCV

There was a significant decrease in PCV and Hb of subgroup C and D male and female when compared with controls. While there is no significant decrease in Hb and PCV of subgroup A and B as compared with controls (table

B). Regarding subgroup A and B the results in this study in agreement with (4) ,while subgroup C and D were less than those showed by (2) .

Biochemical studies

Serum bilirubin

The values of total serum bilirubin and indirect serum bilirubin for all sub groups significantly increased in comparison with controls, and the values of direct serum bilirubin for all subgroups are insignificant increase in comparison with controls (Table C). These results agreed with (17) and (1).

Trace elements

Serum Copper

It is found in this study the results of serum Copper for subgroup A male and female insignificantly increased in comparison with controls(table D) .While subgroup B,C and D patients significantly increased in comparison with controls. These results agreed with (12) .

Serum Zinc

The values of serum Zinc for all subgroups patients significantly decreased in comparison with controls (tableD) .which disagreed with (20) who reported higher plasma Zinc concentrations than those obtained in our study. These differences are most likely due to differences in the characteristics of each population, because feeding habits, the practice of breastfeeding, and socioeconomic status can influence plasma and serum Zinc.

Serum Glutathione

The values of serum Glutathione for both males and female patients subgroups significantly decreased in comparison with controls (table D). These results agreed with (21).

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