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Neonatal indirect hyperbilirubinemia and glucose-6-phosphate dehydrogenase deficiency

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Purpose: This study aimed to determine the prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency among infants with neonatal indirect hyperbilirubinemia (NIH); compare G6PD-deficient and G6PD-normal patients regarding hyperbilirubinemia and need for exchange transfusions (ET); and assess risk factors for ET and kernicterus.

Methods: This is a case-control retrospective study. Medical records of NIH patients admitted to the Pediatric Department, Salmaniya Medical Complex, Bahrain, between January 2007 and June 2010 were reviewed. Data on sex, age at presentation, hospitalization duration, need for ET, hemoglobin (Hb) level, reticulocyte count, direct Coombs test, serum total and indirect bilirubin levels, thyroid function, blood and urine cultures, G6PD status, and blood groups were collected and compared between the G6PD-deficent and G6PD-normal patients.

Results: Of 1,159 NIH patients admitted, 1,129 were included, of whom 646 (57%) were male. Among 1,046 patients tested, 442 (42%) were G6PD deficient, 49 (4%) needed ET, and 11 (1%) had suspected Kernicterus. The G6PD-deficient patients were mainly male ($P<0.0001$), and had lower Hb levels ($P<0.0001$) and higher maximum bilirubin levels ($P=0.001$). More G6PD-deficient patients needed ET ($P<0.0001$). G6PD deficiency ($P=0.006$), lower Hb level ($P=0.002$), lower hematocrit count ($P=0.02$), higher bilirubin level ($P<0.0001$), higher maximal bilirubin level ($P<0.0001$), and positive blood culture result ($P<0.0001$) were significant risk factors for ET. Maximal bilirubin level was a significant risk factor for kernicterus ($P=0.021$) and independently related to ET ($P=0.03$).

Conclusion: G6PD deficiency is an important risk factor for severe NIH. In G6PD-deficent neonates, management of NIH should be hastened to avoid irreversible neurological complications.

Key words: Neonatal hyperbilirubinemia, Glucosephosphate dehydrogenase deficiency, Whole blood exchange transfusion, Kernicterus

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Introduction

Neonatal indirect hyperbilirubinemia (NIH) is a common problem among infants[1,2]. It affects 60% of full-term and 80% of preterm newborns in the first 3 days of life[2]. NIH carries a substantial risk for harmful complications which include long-term neurologic impairments and death[3]. Although significant complications of NIH have become rare in the recent years with therapeutic interventions[3], severe NIH secondary to reduced Glucose 6-phosphate dehydrogenase (G6PD) activity is still complicated by kernicterus which is a serious neurological disease[3-7]. G6PD deficiency is an X-linked recessive disease affecting males more than females[8]. It is common in Bahrain with a prevalence of 22.3%[8]. The relationship between NIH and G6PD deficiency is well established[4,9]. Infants with G6PD

deficiency are at higher risk of mortality secondary to bilirubin encephalopathy if total serum bilirubin (TSB) is ≥40 mg/dL[3]. While spectrums of G6PD-deficient infants in relation to severe NIH have been evaluated in many countries[2-4,9-13], to our knowledge it has not been evaluated in Bahrain.

The aim of this study is to identify the prevalence of G6PD deficiency in newborns with NIH requiring phototherapy, to compare patients with reduced G6PD activity and those with normal G6PD activity in terms of level of indirect hyperbilirubinemia, need for exchange transfusion (ET) and development of kernicterus; and to assess risk factors for ET and kernicterus.

Materials and methods

1. Patients and materials

In this case-control retrospective study, all electronic medical records of NIH patients admitted to the Pediatric Department at Salmaniya Medical Complex, Kingdom of Bahrain, at 2 points in times, were reviewed. The first review was from January 2007 till January 2008 and the second review was from December 2008 to June 2010. The reason for this period gap is that during the study period we realized that similar unpublished data were already collected by different investigators in the same institute for the year of 2007; so the decision to combine the patients' data together after checking for similarity was made. All NIH infant admitted to general pediatric wards were reviewed. Patients were excluded from the study if they were missing data about serum bilirubin, had cholestatic jaundice or missing important data required for the study objectives. Readmissions and duplicate registries were also excluded.

Data about sex, gestational age, age at presentation, and length of hospitalization were collected for all patients. Laboratory evaluations including maternal and newborn blood group and rhesus factor (Rh), hemoglobin (Hb) level, reticulocyte count, direct coombs test (DCT), TSB and indirect serum bilirubin (ISB) levels at admission, maximum TSB and ISB levels, serum free thyroxine (T4) and thyroid stimulating hormone level, blood and urine cultures, erythrocyte G6PD status and Hb electrophoresis were gathered. Needs for double volume whole blood ETs were also included. G6PD test was performed using fluorescence spot test (1 mL of whole blood in ethylenediamine tetraacetic acid tube). Kernicterus was suspected in patients who had early neurological symptoms and signs. Radiological imaging such as skull ultrasound, computed tomography scan and magnetic resonance imaging of the brain were reviewed for those patients.

2. Ethical consideration

This study was conducted in accordance with the principles of Helsinki Declaration and it was ethically approved by the se-

condary care medical research subcommittee, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain.

3. Statistical analysis

The patients' data were analyzed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). The frequencies and percentages were calculated for categorical variables. Chi-square and Fisher exact tests were used to compare categorical variables. Continuous variables were checked for normal distribution using Kolmogorov-Smirnov test. Group data are presented as a mean and standard deviation for normally distributed variables or median and range for nonnormally distributed variables. Due to large sample size, independent Student t test was used to compare continuous variables. G6PD-deficient group was compared with normal-G6PD group in terms of sex, age at presentation, length of hospitalization, Hb level, hematocrit level, reticulocyte count, blood group and Rh incompatibilities, positive DCT, TSB at admission, maximum TSB, need for ET, positive urine and blood cultures, risk for convulsions and suspected kernicterus. These variables were also used to assess the possible risk factors for ET and kernicterus using univariate analysis. Risk factors found to be significant in univariate analysis and have no multicollinearity using a variation inflation factor (VIF) were included in a binary logistic regression to find the independent risk factors of requiring ET or development of kernicterus. The confidence level was set at 95% with 5% confidence interval (CI). P value was considered to be significant if <0.05.

Results

A total of 1,159 admissions were collected in the study periods. Thirty admissions were excluded from the study due to missing data about serum bilirubin in 11 patients, readmissions in 9, duplicate registries in 6; cholestatic jaundice in 3 and 1 patient was excluded due to missing all important data with very low serum bilirubin level (TSB, 97 μmol/L). The remaining 1,129 patients were included. The clinical characteristics and the results of laboratory tests of all newborns included in the study are shown in Table 1. Males were 646 (57%). Out of 1,046 patients tested for G6PD status, 442 (42%) were G6PD-deficient. Hypo and hyperthyroidism were found in 1 patient each. Urine culture was positive in 48 (19%). It grew *Escherichia coli* in 26 (11%), Klebsiella in 17 (7%), *Enterococcus* in 2 (1%), Beta-hemolytic streptococci in 2 (1%) and *Enterobacter* in 1 patient (0.4%). Blood culture was positive in 15 patients (9%). It grew *Staphylococcus aureus* and *E. coli* each in 4 patients (2%), Enterococci and beta-hemolytic streptococci each in 3 patients (2%); and Klebsiella in 1 patient (1%).

All the patients received phototherapy. Out of 49 (4%) who had

double volume whole blood ET, 10 (1%) required ET twice. Packed red blood cell transfusion was required in 48 (4.3%). Eleven patients (1%) were suspected to have bilirubin encephalopathy (kernicterus). The characteristics of these patients are shown in Table 2. Eight patients (1%) developed convulsions during their admission.

On comparing G6PD-deficient with normal-G6PD neonates (Table 3), males were more affected with G6PD deficiency than females (P<0.0001). G6PD-deficient neonates had lower Hb level (P<0.0001), lower hematocrit (P=0.034), higher TSB at admission (P=0.018), higher maximal serum bilirubin (P=0.001) and higher requirement for ET (P<0.0001). They had longer hospital stay (P= 0.05). They also developed more convulsions and suspected kernicterus than normal-G6PD neonates but these were not statistically significant.

In univariate analysis, G6PD deficiency (P=0.006), lower Hb level at admission (P=0.002; 95% CI, 0.4 to 1.8), lower hematocrit level (P=0.02; 95% CI, 0.6 to 6.3), higher TSB at admission (P< 0.0001; 95% CI, -206 to -106), higher maximal TSB (P<0.0001; 95% CI, -205 to -131) and positive blood culture (P<0.0001) were statistically significant risk factors for ET (Table 4). The maximal bilirubin level was the only statistically significant risk factor for suspected kernicterus patients (450±172 µmol/L vs. 316±70.5 µmol/L, P=0.02; 95% CI, -243 to -24).

The significant risk factors for ET were tested to determine multicollinearity (defined as a VIF>8) between each other and were put into a logistic regression model. In this model, the maximal TSB level (P=0.03) was found to be independently related to requirement for ET (Table 5).

Discussion

NIH is a multifactorial disease[9,10]. Any disease that causes increase in bilirubin production and/or reduces conjugation can lead to NIH[2,10]. Hemolytic diseases like ABO incompatibility, Rh incompatibility, spherocytosis and G6PD deficiency can increase bilirubin production while Crigler-Najjar syndrome, hypothy-

Table 1. Clinical characteristics and laboratory results of 1,129 newborns with indirect hyperbilirubinemia

Clinical characteristics and laboratory tests	Value	Total
Male sex	646 (57)	1,129
Gestational age		
Term	1,111 (98)	1,129
Preterm	18 (2)	1,129
Age at presentation (day)	4 (0–64)	1,121
Length of hospitalization (day)	2 (1–100)	1,120
G6PD deficiency	442 (42)	1,046
α−athalassemia	346 (33)	1,052
Hemoglobin (g/dL)	17 (8–24)	1,108
Hematocrit (%)	49 (25-69)	675
Reticulocyte count	3 (0–21)	988
Positive DCT	95 (9)	1,023
ABO incompatibility	132 (42)	316
Rh incompatibility	13 (4)	316
TSB at admission (µmol/L)	292 (69–839)	689
Maximum TSB (µmol/L)	306 (82–952)	1,126
Free T4 (µU/mL)	23 (0–56.9)	1,062
TSH (µU/mL)	3.3 (0–388)	1,071
Positive urine culture	48 (19)	247
Positive blood culture	15 (9)	175

Values are presented as number (%) or median (range).
G6PD, glucose-6-phosphate uridyltransferase enzyme; DCT, direct coombs test, ABO, blood group A, B, and O; Rh, rhesus factor; TSB, total serum bilirubin; T4, thyroxin level; TSH, thyroid-stimulating hormone.

Table 2. Characteristics of patients with neonatal indirect hyperbilirubinemia and suspected kernicterus

Patient	Sex	Symptoms	MTB	ET	Brain radiological findings
1	F	Lethargy and hypotonia	839	2	Brain MRI showed diffuse increase signals in basal ganglia bilaterally on T1
2	F	Lethargy and hypotonia	653	2	Early brain MRI was normal
3	M	One attack of convulsion	566	2	Normal brain ultrasound
4	M	Dyskinesia and hypertonia. Then developed cerebral palsy	515	2	Brain MRI showed bright signal intensities in globus pallidi & substantia nigra bilaterally
5	F	Trisomy 21 patient who was not fixating with light	476	-	Brain MRI showed diffuse volume loss of grey & white matter with dilation of ventricles
6	M	Convulsion	428	2	Normal brain ultrasound
7	M	Focal seizures on left side	392	-	Normal brain MRI. EEG showed focal discharges at the central region
8	M	One attack of convulsion	378	-	Normal brain CT scan
9	F	Convulsions	329	-	Normal brain ultrasound
10	M	Spastic diaplegia, nystagmus & head tremors	315	-	Brain MRI showed mild volume loss affecting periventricular white matter
11	F	Five attacks of convulsions	345	-	Normal brain MRI

MTB, maximum total bilirubin in µmol/L; ET, exchange transfusion; MRI, magnetic resonance imaging; EEG, electroencephalogram; CT, computed tomography.

Table 3. Comparison between the G6PD-deficient and G6PD-normal newborns with indirect hyperbilirubinemia

| Variable | G6PD status (n=1,046) | | Total | 95% CI | P value* |
	Normal (n=604)	Deficient (n=442)			
Male sex	271 (45)	324 (73)	1,046	-	<0.0001
Age at presentation (day)	4.5±4.1	4.3±2.6	1,038	-0.3 to 0.6	0.5
Length of hospitalization (day)	3.1±2.4	3.7±5.7	1,037	-1.2 to -0.001	0.05
Hemoglobin (g/dL)	16.9±2.4	16.4±2.2	1,032	0.3 to 0.8	<0.0001
Hematocrit (%)	49.6±7	48.4±6.6	639	0.1 to 2.3	0.03
Reticulocyte (%)	3.4±2.7	3.3±2.2	919	-0.2 to 0.5	0.3
ABO incompatibility	75 (44.6)	53 (39.3)	316	-	0.4
Rh incompatibility	5 (3.0)	4 (3.0)	316	-	1
Positive DCT	67 (12.1)	23 (5.7)	955	-	0.003
Total bilirubin at admission (μmol/L)	284±70	298±76	649	-25 to -2	0.02
Maximal bilirubin level (μmol/L)	313±67	327±81	1,043	-24 to -6	0.001
Positive urine culture	23 (3.8)	18 (4.1)	224	-	0.6
Positive blood culture	6 (1.4)	9 (3.2)	161	-	0.2
Exchange transfusion	18 (3.0)	29 (6.6)	1,046	-	0.01
One exchange	14 (2.3)	23 (5.2)	1,046	-	0.02
Two exchanges	4 (0.7)	6 (1.4)	1,046	-	0.3
Convulsions	3 (0.5)	5 (1.1)	1,046	-	0.3
Suspected kernicterus	5 (0.8)	6 (1.6)	1,046	-	0.5

Values are presented as number (%) or mean±standard deviation.
G6PD, glucose 6 phosphate uridyltransferase enzyme; CI, confidence interval; ABO, blood group A, B, and O; Rh, rhesus factor; DCT, direct Coombs' test.
*Student t test was used for continuous variables and chi-square or Fisher exact test were used for categorical variables.

Table 4. Univariate analysis of the predicted risk factors for the need of exchange transfusion in 1,129 newborns with indirect hyperbilirubinemia

| Variable | Exchange transfusion | | Total | 95% CI | P value* |
	Yes (n=49)	No (n=1,080)			
Male sex	26 (53)	620 (57)	1,129	-	0.6
Age at presentation (day)	3.6 (2)	4.4 (4)	1,121	-0.3 to -2	0.1
Length of hospitalization (day)	5.8 (3)	3.2 (4)	1,120	-3.7 to -1.5	<0.0001
Hemoglobin (g/dL)	15.6±2.6	16.7±2.4	1,108	0.4 to 1.8	0.002
Hematocrit (%)	46±7	49±7	675	0.6 to 6.3	0.02
Reticulocyte count (%)	4 (4)	3 (2)	988	-2 to 0.4	0.2
G6PD deficiency	29 (62)	413 (41)	1,046	-	0.006
ABO incompatibility	19 (39)	113 (42.3)	316	-	0.8
Rh incompatibility	4.0 (8)	9 (3.4)	316	-	0.1
Positive DCT	5 (11.6)	90 (9.2)	1,023	-	0.6
Total bilirubin at admission (μmol/L)	438±121	283±63	689	-206 to -106	<0.0001
Maximal bilirubin level (μmol/L)	478±128	310±61	1,126	-205 to -131	<0.0001
Positive urine culture	2 (4.1)	46 (4.3)	247	-	0.4
Positive blood culture	12 (25)	3 (0.4)	175	-	<0.0001

Values are presented as number (%) or mean±standard deviation.
G6PD, glucose 6 phosphate uridyltransferase enzyme; CI, confidence interval; ABO, blood group A, B, and O; Rh, rhesus factor; DCT, direct Coombs' test.
*Student t test was used for continuous variables and chi-square or Fisher exact test were used for categorical variables.

roidism and prematurity can reduce conjugation[2]. Breast milk feeding may also act as a modifier that predisposes the risk for development of severe NIH with a specific genotype[14]. Unconjugated bilirubin is mainly produced by erythrocytes turnover[15].

Hemolysis, which is a frequent cause of NIH, results in increased serum free Hb which is metabolized to produce more bilirubin[5,15].

G6PD is one of the antioxidant enzymes that protect the cell from injury[7,8,12]. G6PD deficiency is estimated to affect 200

Table 5. Binary logistic regression analysis of the selected risk factors for the need of exchange transfusion in 1,129 newborns with indirect hyperbilirubinemia

Variable	Adjusted odd ratio	95% CI	P value
Length of hospitalization (day)	0.76	0.5 to 1.1	0.19
Hemoglobin (g/dL)	0.77	0.3 to 1.9	0.58
Hematocrit (%)	0.97	0.7 to 1.3	0.84
G6PD deficiency	0.13	0.01 to 1.5	0.09
Total bilirubin at admission (µmol/L)	0.99	0.9 to 1	0.92
Maximal bilirubin level (µmol/L)	1.04	1 to 1.08	0.03
Positive blood culture	0.37	0.01 to 11	0.57

Data of selected risk factors for the need of exchange transfusion that were found to be significant in univariate analysis and do not have multicollinearity using variation inflation factor >8.
CI, confidence interval; G6PD, glucose 6 phosphate uridyltransferase enzyme.

million individuals worldwide[9]. It is more common in the Mediterranean area, Middle East, India, China, and Africa[8]. G6PD deficiency is an independent risk factor for high serum bilirubin level ≥18 mg/dL[10]. It is considered as one of the most common clinically significant enzyme defects[4,8,9]. G6PD-deficient individuals are usually healthy and asymptomatic but acute hemolysis may occur after ingestions of certain drugs, food, exposure to certain chemicals, infections or hypoxia[7-9,13]. They could be attributable to the early onset hemolysis due to oxidative stress as a result of perinatal events[12]. Chronic nonspherocytic hemolytic anemia may rarely occur[7-9].

Our study showed that G6PD deficiency is a common problem among NIH infants in a Middle East country like Bahrain. The prevalence of G6PD deficiency in NIH patients also varies in different parts of the world[2,4,12,16]. NIH is more common to occur in Asian and African than in European G6PD deficient newborns[7,9]. In Turkey, the prevalence of G6PD deficiency is only in 1%–5% of the population with male to female ratio is 3:1 and 3.8% of NIH infants are G6PD deficient[4]. In our study, we found that 42% of NIH patients were G6PD-deficient which is double compared to general population (22%)[8]. Similar to other studies[3,7], our study showed that most of G6PD-deficient newborns were males (73%).

A protocol for assessment of NIH should be established in nurseries[6]. Systematic assessment for risk of severe NIH, close follow up and prompt intervention are important to prevent complications[6]. There is a high concern that underrecognition and inadequate investigation of severe NIH in otherwise healthy neonates contribute to early readmission and potential long-term complications, including bilirubin-induced encephalopathy and kernicterus[17]. Every effort should be made to detect newborns at risk of severe NIH before discharge from hospital[17]. Yellowness of lower extremities, palms and soles noticed on visual assessment by health care workers is significantly associated with a high serum bilirubin level[1]. In a well-lit room or day light, NIH can be identified by blanching the skin with digital pressure to visualize

the underlying color of the skin and subcutaneous tissue[6]. However, visual assessment of bilirubin level via the degree of jaundice can lead to error, particularly in infants with dark skin[6].

Transcutaneous bilirubin (TcB) nomogram is offered as a tool that can help the clinician in the management of NIH[18]. TcB devices are more accurate than visual inspection, can save time and money and in many times spares neonate from an invasive procedure[18]. TcB is accepted to be used to diagnose and monitor NIH but it might be less accurate when TSB is rapidly increasing due to the lag time between tissue and serum bilirubin[18].

Further investigations like G6PD tests and follow-up planning could be carried out to assess the risk of and to prevent severe NIH if serum bilirubin level was checked at the time of discharge from hospital[17]. Early detection of G6PD deficiency via newborn screening is feasible, cost effective and allows early prevention of severe NIH and kernicterus[8]. G6PD deficiency should be confirmed by rapid fluorescent spot test or quantitative spectrophotometry of red blood cell enzyme activity when clinical and hematological findings are suspicious[7]. G6PD c.563C>T mutation is a significant risk factor for early development and moderately severe NIH[11].

In our study, G6PD-deficient neonates were found to have lower Hb and hematocrit levels compared to normal-G6PD neonates. Similar to our study, Moiz et al.[11] found significant differences in Hb level and reticulocyte counts in G6PD-deficient compared to normal newborns. Weng and Chiu[3] also showed that G6PD-deficient infants had lower Hb level with an evidence of hemolysis. Lower Hb level in G6PD-deficient newborn is associated with higher peak serum TSB level[3]. Like our study, Atay et al.[4] found that TSB at presentation and the maximum level were higher in the G6PD-deficient compared to normal patients. Furthermore, in a case-control study, Kaplan and Abramov[13] showed that G6PD-deficient neonates are more prone to develop NIH, require phototherapy and their hematocrit levels are lower. In Ainoon et al. study[9], out of 38 G6PD-deficient neonates, 63% had NIH and 28.9% had moderate to severe NIH that required phototherapy or ET. However, Koosha and Rafizadeh[2] studied 376 newborns with NIH and showed no statistical differences in the lowest Hb level, reticulocyte count and highest TSB, between G6PD-deficient and normal newborns. Atay et al.[4] also found no difference in hematocrit level and reticulocytes count between G6PD-deficient and normal neonates.

NIH secondary to G6PD deficiency is treated like NIH due to other causes[7]. Phototherapy or ET are the recommended treatment to prevent the development of severe NIH and possibly kernicterus[6,7,12]. Despite intensive phototherapy, severe NIH may still need ET to prevent bilirubin encephalopathy[12]. Our study showed that G6PD deficiency is a significant risk factor for the need of ET. In addition, it has been proven that infants with idiopathic NIH showed unexpected rise in serum TSB after ET if

the donor blood was G6PD deficient[12]. Elevated serum bilirubin due to ongoing subclinical hemolysis might lead to phototherapy continuation and possible repeat of ET[12]. Therefore, donor blood should be screened for G6PD status before using it for ET in countries where G6PD deficiency is prevelant[12]. This test is not routinely performed in Bahrain.

In this study, G6PD-deficient neonates had significantly higher TSB compared to G6PD-normal newborns. Although rare, significant NIH poses a possible risk for permanent neurological deficit or kernicterus[7,11]. G6PD deficiency can cause severe NIH that can lead to kernicterus[2,4,6]. In acute or chronic bilirubin encephalopathy, kernicterus was originally characterized by pathological bilirubin staining of the brainstem nuclei and cerebellum[6]. Acute toxicity of the basal ganglia and various brainstem nuclei by bilirubin within the first week of life will lead to clinical central nervous system findings of bilirubin encephalopathy[6]. Kernicterus is a preventable complication[6]. The resurgence of a largely preventable disease like kernicterus secondary to severe NIH is of a great concern[17]. The duration of phototherapy can be used as a surrogate marker for the severity of NIH but it can be shortened by ETs[10].

In conclusion, G6PD deficiency is a common disease in infants with NIH. It is considered an important risk factor for severe NIH which may result in kernicterus. In infants with G6PD deficiency, management of NIH should be hastened to avoid irreversible neurological complications. Further studies are required to evaluate the relationship between the G6PD enzyme level and the severity of NIH and to set a preventive protocol to avoid the neurological impairment for newborns at risk.

This study was limited by the lack of data about birth weight and by its' retrospective nature. Another limitation is that we may have included G6PD-deficient newborns within the normal group because testing for G6PD may be falsely negative during acute hemolysis[12] and in heterozygous female newborns[8] where lionization phenomena can occur. In addition, this study was limited by the lack of the exact levels of G6PD enzyme activity for all G6PD-deficient newborns. However, Ainoon et al.[9] found no significant association between the level of enzyme activity and the severity of NIH. This study can help the clinicians to screen and allow early treatment for newborns at risk. Early treatment will not only reduce the incidence of severe NIH and kernicterus but also minimize the risks of unintentional harm such as maternal anxiety, reduced breast feeding and unnecessary costs or treatment[6].

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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