Neonatal adrenal hemorrhage: a retrospective study of 16 cases.

Abstract:

Background: Neonatal adrenal hemorrhage is a rare but potentially severe condition of the neonatal period, whose true incidence is likely underestimated because many cases are asymptomatic.

Objective: To describe the epidemiological, clinical, biological, sonographic, therapeutic and outcome characteristics of neonatal adrenal hemorrhage.

Methods: A retrospective descriptive study was conducted in the Neonatology and Neonatal Intensive Care Unit of Hassan II University Hospital, Fez, including all neonates diagnosed with adrenal hemorrhage on renal ultrasound between January 1, 2012 and December 31, 2017.

Results: Sixteen cases were identified among 7610 admissions (incidence 2/1000). Male predominance was noted (62.5%). Fundal pressure during delivery was reported in 87.5% of vaginal deliveries. The main admission diagnoses were perinatal asphyxia and jaundice (31.25% each). Jaundice (56.25%), abdominal mass (50%) and hypotonia (56.25%) were the leading clinical signs. Anemia was found in 37.5% and severe hyperbilirubinemia in 18.75%. Abdominal ultrasound showed right-sided hemorrhage in 50%, left-sided in 31.25%, and bilateral in 18.75%, with lesion size ranging from 17 to 50 mm. Adrenal insufficiency complicated bilateral hemorrhage in 3 cases. Treatment was mainly supportive; outcome was favorable in 81.25%, with a mean sonographic resolution time of 55 days, while 3 deaths (18.75%) occurred, mostly in bilateral forms.

Conclusion: Neonatal adrenal hemorrhage should be systematically screened for by abdominal ultrasound in the presence of atypical jaundice, abdominal mass, or perinatal risk factors (fundal pressure, asphyxia, macrosomia), to allow early detection of adrenal insufficiency, a rare but severe complication of bilateral forms.

Keywords: neonatal jaundice, adrenal insufficiency, renal ultrasound, adrenal hemorrhage

1. Introduction

Neonatal adrenal hemorrhage is a rare condition of the neonatal period that may be clinically severe, warranting systematic investigation in the presence of risk factors [1]. It may be of traumatic or non-traumatic origin.

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Traumatic Neonatal adrenal hemorrhage is related to difficult extraction and to fundal pressure applied during delivery. In non-traumatic forms, the risk factors classically reported are perinatal asphyxia, maternal-fetal infection, high birth weight [1,2,3,4], and antenatal or postnatal renal vein or inferior vena cava (IVC) thrombosis [5].

The physiological hypervascularization of the adrenal glands during the neonatal period accounts for the relative frequency of NAH at this age. The right adrenal gland is preferentially affected [3,6,7,8,9,10] because of its close anatomical relationship with the liver, the IVC and the right renal vein [11,12], which favors transmission of venous pressure changes to the gland and consequent bleeding [13,14].

Abdominal ultrasound is the reference examination for diagnosing and monitoring NAH [11,15,16,17]. Severe hyperbilirubinemia [18,19] and acute adrenal insufficiency, particularly in bilateral disease, remain its most feared complications [2,3].

We report a retrospective study conducted in the Neonatology and Neonatal Intensive Care Unit of Hassan II University Hospital, Fez, including all neonates diagnosed with adrenal hemorrhage between 2012 and 2017, with the aim of describing the clinical features, sonographic findings, laboratory profile, risk factors, management and outcome of this condition.

2. Materials and methods

2.1. Study design and population

This was a retrospective descriptive study conducted in the Neonatology and Neonatal Intensive Care Unit of Hassan II University Hospital, Fez, covering the records of all neonates in whom adrenal hemorrhage was diagnosed on renal ultrasound over a six-year period, from January 1, 2012 to December 31, 2017.

All neonates who underwent a renal ultrasound demonstrating adrenal hemorrhage were included, regardless of the reason for admission.

2.2. Data collection

Data were collected from departmental registers, clinical charts and ultrasound reports using a standardized data-collection form recording maternal and neonatal characteristics, history, pregnancy and delivery data, clinical examination, laboratory work-up, imaging findings, treatment received and outcome.

All patient's identification was de-identified

2.3. Statistical analysis

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Data were entered and analysed using Microsoft Excel (Microsoft office 2019). Quantitative variables are expressed as means ± standard deviations, and qualitative variables as counts and percentages.

3. Results

3.1. Epidemiology

3.1.1. Incidence

During the six-year study period, 7610 neonates were admitted to the unit. Sixteen of them (0.2%) had adrenal hemorrhage, giving a hospital incidence of 2 per 1000 admissions.

2012	2013	2014	2015	2016	2017
2 cases	3 cases	4 cases	2 cases	3 cases	2 cases

Table 1: Annual distribution of adrenal hemorrhage cases.

3.1.2. Sex distribution

A male predominance was observed, with 62.5% of boys (N=10) versus 37.5% of girls (N=6), giving a sex ratio of 1.7.

3.1.3. Age at admission

Age at admission ranged from 4 hours to day 25 of life; most infants (6 of 16) were admitted between 24 and 72 hours of life.

3.2. History

Parental consanguinity was found in 12.5% (N=2). Maternal age ranged from 18 to 45 years (mean 28 years). Two mothers had a chronic condition under treatment during pregnancy (pre-eclampsia on methyldopa; ulcerative colitis on mesalazine); the infant of the latter was born with extensive renal vein thrombosis extending to the IVC, complicated by NAH.

Regarding parity, 31.25% (N=5) of mothers were primiparous, 25% (N=4) paucigravid and 43.75% (N=7) multiparous. Eleven pregnancies (68.75%) were medically followed, with negative screening serologies in all cases. All infants were born at term. Delivery was vaginal in 87.5% (N=14) of cases and by cesarean section in 12.5% (N=2). Mean labor duration was 13 hours. Fundal pressure was applied in

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all vaginal deliveries. Poor adaptation to extrauterine life requiring resuscitation was noted in 31.25% (N=5) of neonates.

3.3. Reasons for admission

The two leading admission diagnoses were perinatal asphyxia and jaundice, each found in five neonates (31.25%), followed by fever in three (18.75%), maternal-fetal infection in two (12.5%) and malformative uropathy in one patient (6.25%).

3.4. Clinical findings

Admission weight ranged from 2600 to 4100 g (mean 3454.6 g), length from 45 to 55 cm (mean 48 cm), and head circumference from 30 to 40 cm (mean 34 cm).

Clinical sign	Number of cases	Percentage
Jaundice	9	56.25%
Hypotonia	9	56.25%
Abdominal mass	8	50%
Feeding difficulty	6	37.5%
Pallor	5	31.25%
Fever	5	31.25%
Respiratory distress	5	31.25%
Bone fracture	1	6.25%
Scrotal hematoma	1	6.25%

Table 2: Clinical signs observed

NAH was associated with dehydration in one patient and was found in a neonate with trisomy 21. A left scrotal hematoma associated with NAH was found in one patient, confirmed by transillumination.

3.5. Laboratory findings

Total bilirubin (measured in 9 patients) ranged from 50 to 337 mg/L, with severe hyperbilirubinemia (>180 mg/L) in 3 neonates (18.75%). Hemoglobin was low in 6 patients (37.5%), averaging 11.82 g/dL. Serum sodium (measured in 11 patients) averaged 139 mmol/L, with hyponatremia in 3 patients (18.7%) and hypernatremia in

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1 (6.25%). Serum potassium (measured in 11 patients) averaged 5.28 mmol/L, with hyperkalemia in 4 patients (25%). Blood glucose (measured in 13 patients) averaged 0.57 g/L, with hypoglycemia in 3 patients (18.7%). CRP was elevated in 9 patients (56.25%). TSH, measured in 2 patients, confirmed hypothyroidism in both. Urinary catecholamines, measured in 3 patients, were normal in all. Urine culture, performed in 10 patients, was positive for Escherichia coli in 3; blood cultures were negative in all patients, and lumbar puncture, performed in 3 patients, was negative.

3.6. Imaging

3.6.1. Abdominal ultrasound

Performed in all patients, abdominal ultrasound showed right-sided NAH in 8 cases (50%), left-sided in 5 (31.25%), and bilateral in 3 (18.75%), with lesion size ranging from 17 to 50 mm.

Location	Number of cases	Percentage
Right-sided NAH	8	50%
Left-sided NAH	5	31.25%
Bilateral NAH	3	18.75%

Table 3: Sonographic location of adrenal hemorrhage

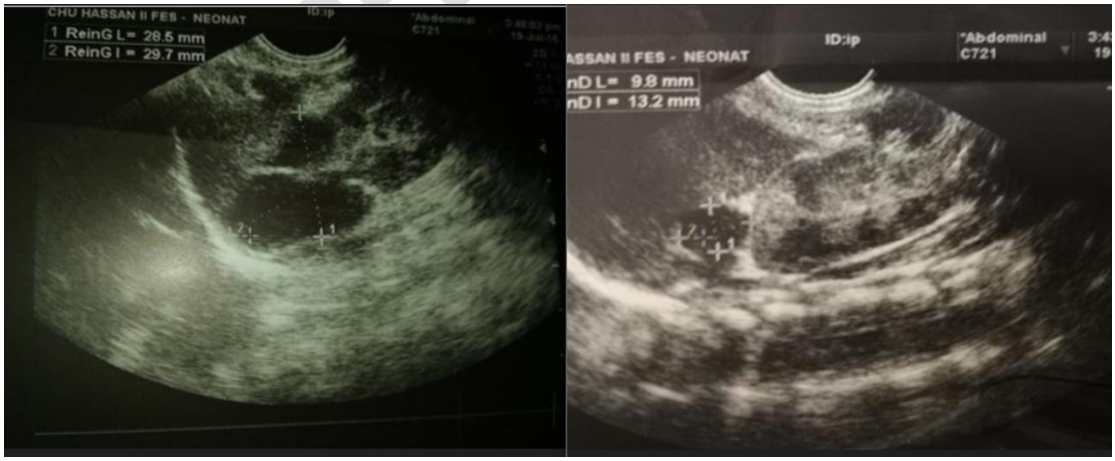


Figure 1: Renal ultrasound (patient 11) showing bilateral adrenal hemorrhage

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Figure 2: Renal ultrasound (patient 16) showing bilateral adrenal hemorrhage.

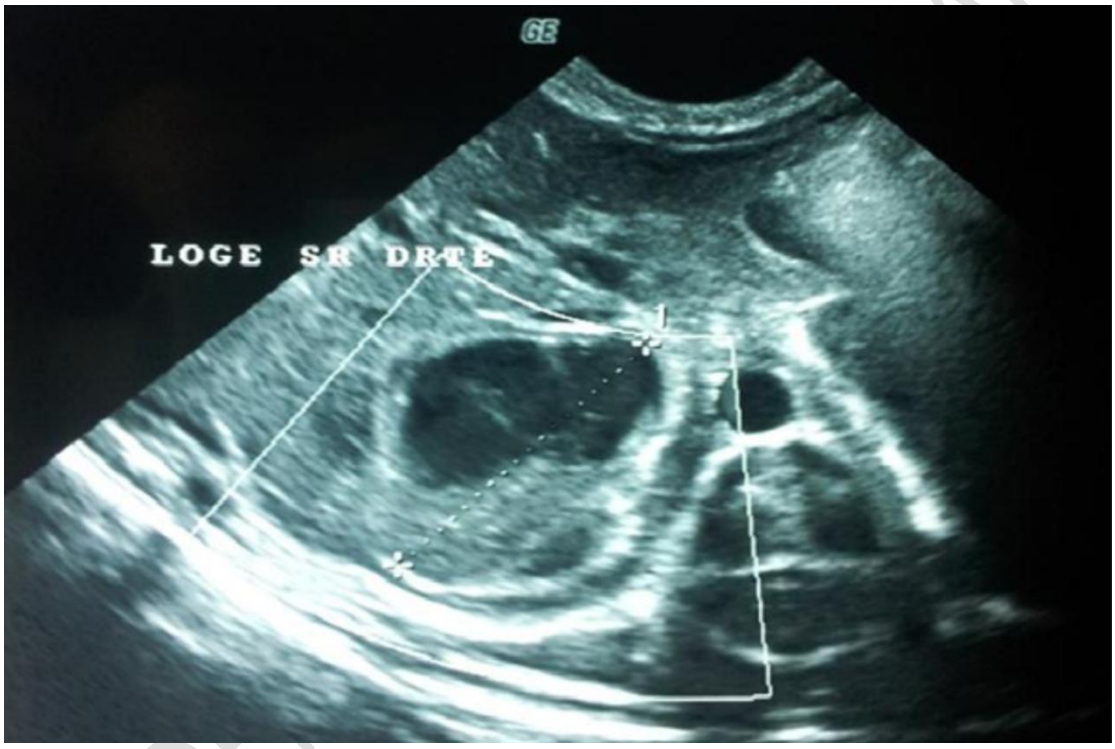


Figure 3: Renal ultrasound (patient 5) showing right-sided adrenal hemorrhage

3.6.2. Other imaging studies

Abdominal CT, performed in doubtful cases or those associated with thrombosis, confirmed the diagnosis in 4 patients and showed IVC thrombosis extending to the renal veins in 2, also confirmed by renal vein Doppler ultrasound. Transfontanellar ultrasound (2 cases), cerebral CT (2 cases) and transthoracic echocardiography (2 cases) were performed selectively, revealing cerebral edema, cerebral ischemia and hypertrophic cardiomyopathy, respectively, in a single patient who had an unfavorable outcome.

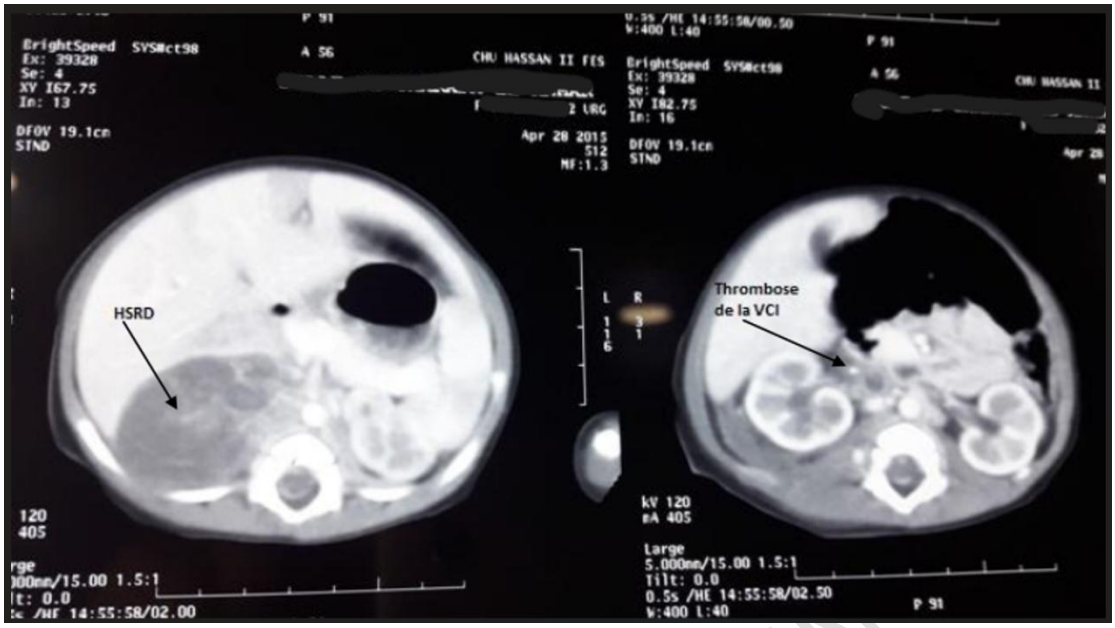


Figure 4: Abdominal CT (patient 15) showing right-sided adrenal hemorrhage with IVC thrombosis extending to both renal veins

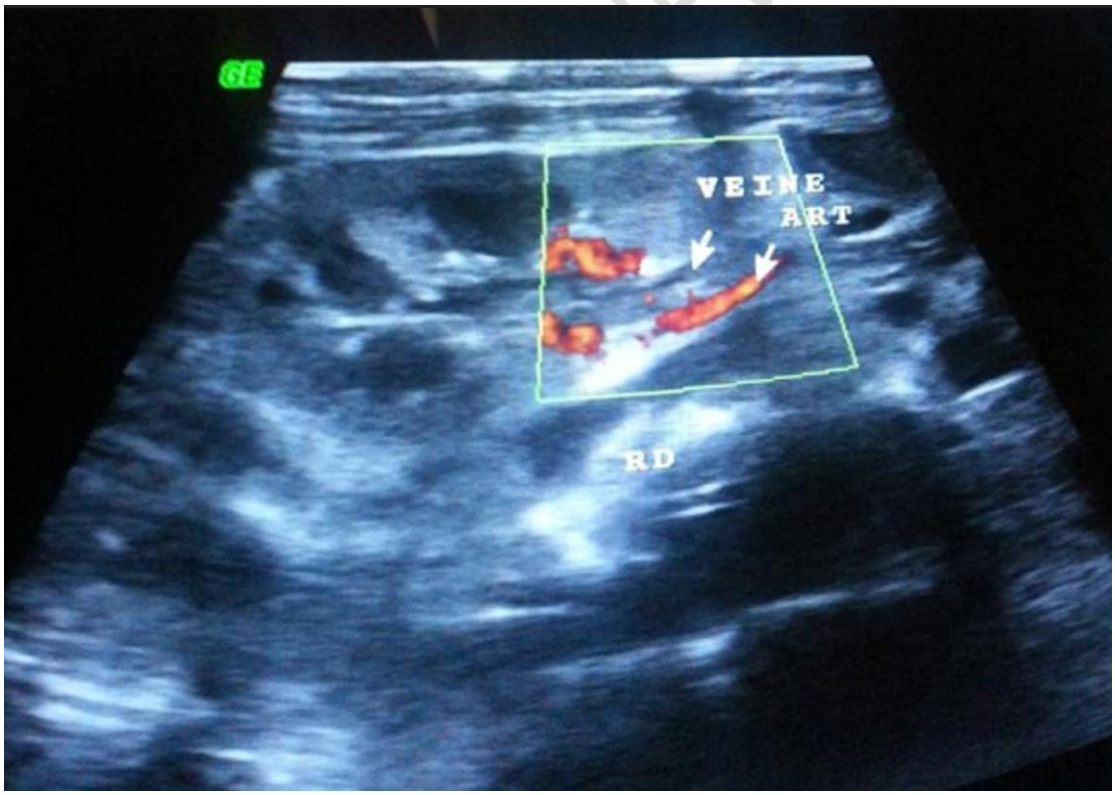


Figure 5: Renal vein Doppler ultrasound (patient 14) showing left renal vein thrombosis

3.7Treatement

Therapeutic measure	Number of cases	Percentage
Dual antibiotic therapy (3rd-gen. cephalosporin + aminoglycoside)	16	100%
Phototherapy	5	31.25%
Exchange transfusion	2	12.5%
Packed red-cell transfusion	1	6.25%
Phenobarbital	3	18.75%
Hydrocortisone	3	18.75%
Fluid and electrolyte correction	3	18.75%

Table 4. Therapeutic modalities.

3.8. Follow-up and outcome

Length of hospital stay ranged from 3 to 20 days (mean 6 days). Outcome was favorable in 13 patients (81.25%). Three patients (18.75%) died, 2 (12.5%) of whom had bilateral NAH. Adrenal insufficiency was observed only in the three (18.75%) neonates with bilateral disease; the only survivor among them received hydrocortisone for 4 weeks. Sonographic follow-up showed complete resorption of the hematomas after 27 days to 2 months and 11 days, averaging 55 days.

4. Discussion

4.1. Epidemiology and risk factors

NAH is a rare condition favored by the relatively large size and extensive vascularization of the adrenal gland during this period of life, which make it vulnerable to trauma and asphyxial injury [20]. In our series, the hospital incidence was 0.21%, comparable to that reported by Felc [20] but markedly lower than that reported by Gyurkovits [21] (1.9%), a difference plausibly explained by systematic screening ultrasound in the latter cohorts, which detects asymptomatic forms, whereas in our series ultrasound was performed only when clinically indicated. The male predominance observed here is consistent with the literature [2,21,20,22,23], as is the predominance of term neonates delivered vaginally [3,24].

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Fundal pressure, an uncodified obstetric maneuver rarely documented in the delivery record despite its risk of maternal-fetal trauma, was recorded in 87.5% of our vaginal deliveries - comparable to the rate reported by the Casablanca group [1]. No study has yet established a direct causal link between this maneuver and NAH, however, which warrants cautious interpretation and dedicated prospective evaluation. Some series report a higher incidence of NAH among macrosomic neonates [25], although most of our patients had a normal birth weight.

Series	Period	Admissions	Cases	M:F	Vaginal delivery
Gyurkovits [21]	13 y	26,416	74	45:29	95.9%
Mutlu [2]	–	–	13	10:3	–
Yao [22]	–	–	28	17:11	71.4%
Felc [20]	2 y	8,474	16	10:6	93.75%
Our series	6 y	7,610	16	10:6	87.5%

Table 5: Comparison with published series: incidence, sex ratio and mode of delivery

4.2. Clinical and laboratory features

Symptoms of NAH are nonspecific and often absent, which explains the frequent underdiagnosis of this condition [10]. The most common presenting sign is jaundice, usually unusually intense or prolonged and without an obvious immunological or infectious cause [26]; it results from resorption of the hematoma, generating predominantly unconjugated hyperbilirubinemia. Any atypical neonatal jaundice should therefore prompt abdominal ultrasound to look for NAH [1]. Pallor reflects the blood loss associated with adrenal bleeding, while a palpable abdominal mass with lumbar contact - whose detection depends on examiner experience - should raise suspicion, particularly when associated with jaundice or pallor. Scrotal hematoma, resulting from blood tracking through the retroperitoneal spaces and the processus vaginalis, is a rare but suggestive sign [24]. Normochromic, normocytic regenerative anemia and predominantly unconjugated hyperbilirubinemia are the main laboratory abnormalities, reflecting blood loss and post-hemorrhagic hematoma resorption, respectively.

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Series	Jaundice	Pallor	Resp. distress	Abd. mass	Scrotal hematoma	Anemia	Hyper-bilirubinemia
Gyurkovits [21]	8.1%	–	–	–	8%	8.1%	50%
Mutlu [2]	85%	38.4%	23.07%	38%	15%	38.4%	–
Yao [22]	28.57%	10.71%	7.14%	–	7.14%	–	–
Felc [20]	75%	31.3%	–	–	6.25%	31.3%	75%
Our series	56.25%	37.5%	31.25%	50%	6.25%	37.5%	62.5%

Table 6: Clinical and laboratory features compared with published series

Acute adrenal insufficiency is rarely reported after NAH, as hormonal impairment classically occurs only once more than 90% of adrenal tissue is destroyed, the hemorrhage usually being subcapsular [11]; the gland's substantial regenerative capacity explains why most adrenal hematomas are not accompanied by significant adrenal insufficiency [2]. Its occurrence may nonetheless be favored by associated risk factors such as prematurity, sepsis, disseminated intravascular coagulation, perinatal hypoxia or intraventricular hemorrhage [1], through mechanisms that may include cytokine-mediated suppression of ACTH or cortisol synthesis, impaired glandular perfusion, limited corticosteroid reserves, or immaturity of the hypothalamic-pituitary-adrenal axis. In our series, adrenal insufficiency occurred exclusively in neonates with bilateral disease, at a higher overall rate (18.75%) than in most published series, likely reflecting our small sample size and a symptom-driven rather than screening-based diagnostic strategy.

4.3. Imaging and differential diagnosis

Abdominal ultrasound remains the reference examination for diagnosing adrenal hematoma: it defines the site, laterality, extent and size of the lesion, screens for other sites of hemorrhage and for associated renal or IVC thrombosis, and allows follow-up until complete resorption [11,15,17,26]. CT is reserved for doubtful cases or those complicated by thrombosis. As in other published series [6,7,22,27], right-sided involvement predominated in our series, reflecting the gland's anatomical position between the liver and spine and its direct venous drainage into the IVC - unlike the left gland, drained by the renal vein - which makes it more sensitive to changes in central venous pressure transmitted directly to its parenchyma [12,28].

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Series	Right	Left	Bilateral	Adrenal insufficiency
Gyurkovits [21]	48.7%	45.9%	5.4%	1.3%
Mutlu [2]	53.8%	7.69%	38.4%	30.76%
Yao [22]	82.1%	17.8%	0%	0%
Felc [20]	81.26%	12.5%	6.25%	6.25%
Our series	50%	31.25%	18.75%	18.75%

Table 7: Laterality and adrenal insufficiency compared with published series

The main differential diagnosis of NAH is adrenal neuroblastoma, a rare malignant embryonal tumor of the sympathetic nervous system that accounts for only 5% of all childhood neuroblastomas in its neonatal form. Diagnosis relies on CT imaging and urinary catecholamine assay (vanillylmandelic and homovanillic acid). Ultrasound usually distinguishes the two entities: neuroblastoma appears as a solid, echogenic, homogeneous mass, whereas NAH is initially homogeneous and progressively evolves toward a cystic appearance [24]; metastatic presentation - notably Pepper syndrome - occurs in 25% of cases before one month of age. In our series, urinary catecholamines, measured in 3 patients, were normal in all.

4.4. Management and outcome

Treatment of NAH is essentially supportive, combining management of jaundice (phototherapy, exchange transfusion) and anemia (transfusion if poorly tolerated), correction of fluid and electrolyte disturbances, and antibiotic therapy for associated infection. When present, adrenal insufficiency is treated with glucocorticoid replacement, essential in case of decompensation [1]. In situations of stress (fever, trauma, surgery), the infant should be considered at risk of adrenal insufficiency and treated with hydrocortisone until complete resorption of the hematoma and normalization of the hormonal work-up [11].

Series	Phototherapy	Transfusion	Antibiotics	Hydrocortisone
Gyurkovits [21]	50%	–	–	1.3%
Mutlu [2]	–	–	–	30.76%
Felc [20]	75%	31.25%	18.75%	6.25%
Our series	31.25%	6.25%	100%	18.75%

Table 8: Therapeutic modalities compared with published series

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Repeated, usually fortnightly, ultrasound monitoring is required to follow the size and echostructure of the lesion. Complete resorption of NAH classically occurs between 3 weeks and 6 months across published series [3,19], consistent with the mean 55-day resolution time observed in our series.

4.5. Limitations

This study has the limitations inherent to a retrospective, single-center design with a small sample size, which precludes formal statistical comparison between subgroups. Because ultrasound was performed only in the presence of clinical signs rather than systematically, our series probably underestimates the true incidence of NAH by missing paucisymptomatic or asymptomatic cases.

5. Conclusion

Neonatal adrenal hemorrhage, although rare, remains a potentially severe condition that should be systematically sought in the presence of perinatal risk factors, notably fundal pressure, perinatal asphyxia, maternal-fetal infection, macrosomia, or renal or caval venous thrombosis. Its clinical manifestations, dominated by the triad of jaundice, anemia and a palpable abdominal mass, remain inconsistent and nonspecific, exposing the condition to underdiagnosis. Abdominal ultrasound remains the key examination for positive diagnosis, lesion characterization and follow-up, and the outcome is most often favorable with spontaneous resorption within a few weeks. Adrenal insufficiency, a rare but potentially severe complication, should be systematically sought in bilateral disease so that appropriate hormone replacement therapy can be started early.

6. References

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