Paediatr Croat. 2014;58:101-106
IZVORNI ZNANSTVENI RAD / *ORIGINAL SCIENTIFIC PAPER*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2014.18

Intracranial hemorrhage due to late vitamin K deficiency in infants in Albania

Ilirjana Klironomi[1], Ermela Celaj[1], Elmira Kola[1], Robert Lluka[1], Durim Sala[1], Irena Kito[1], Durim Celaj[2], Inva Gjeta[1], Sashenka Sallabanda[1]

With vitamin K prophylaxis, late vitamin K deficiency bleeding disease (VKDB) has been reduced, but can still occur and in 50% of cases it presents with intracranial hemorrhage (ICH). We emphasize that vitamin K prophylaxis prevents the classical form of hemorrhagic disease and to a lesser extent prevents late VKDB. Our aim is to increase the awareness of late VKDB in all pediatricians. Data on seven infants treated for ICH due to late VKDB in Albania during January-December 2012 are analyzed. Diagnosis was made according to the International Consensus definition of VKDB. We evaluated clinical presentation, time to diagnosis, coagulation data, hospital course and outcome. During the one-year period, there was an increase in the incidence of late VKDB in Albania, presented with ICH in ≈20/100 000 live births, even with the vitamin K 1 mg i.m. prophylaxis in the first hour of life. The most frequent presenting complaints were seizures (100%) and vomiting (42.8%). The most frequent examination findings were coma (85.7%) and fontanelle bulging (71.4%). Radiologic findings varied and included subdural (71.4%), parenchymal (14.3%) and intraventricular (14.3%) findings. Only one patient underwent surgery for ICH evacuation. Delayed diagnosis was recorded in two cases (28.6%), both died. In conclusion, prophylaxis with vitamin K 1 mg i.m. at birth may be insufficient to prevent late VKDB. Pediatricians should keep in mind the probability of VKDB in infants because early recognition and management are important to decrease the mortality associated with VKDB.

Keywords: vitamin K-deficiency, therapy; intracranial hemorrhages

INTRODUCTION

Intracranial hemorrhage (ICH) is a frequent manifestation of vitamin K deficiency in infancy (1-5). It is the presenting symptom in approximately 50% of cases with late vitamin K deficiency bleeding disease (VKDB) in Western Europe, with even higher rates (up to 82%) in developing countries (1-3, 6, 7). VKDB results in death and severe disability in 33% of affected newborns (4). With vitamin K prophylaxis, late VKDB has been reduced, but still remains a concern in the 21st century because it is a potentially life-threatening bleeding disorder.

Through our reports, we would like to emphasize that vitamin K prophylaxis prevents the classical form of hemorrhagic disease and to a lesser extent prevents late VKDB. On the other hand, we would like to increase the awareness of late VKDB in all pediatricians.

METHODS

Data on seven infants treated for ICH due to late VKDB in Albania during one year (January 2012 – December 2012) were analyzed. Late intracranial VKDB was defined as intracranial bleeding and confirmed using computer tomography (CT) or magnetic resonance imaging (MRI) in infants aged 8 days to 6 months, when the prothrombin assay results were grossly abnormal compared with the standards for age: international normalized ratio (INR) ≥4 control value, prothrombin time (PT) ≥4 control value, and at least one

[1] PICU, UHC "Mother Theresa", Tirana, Albania
[2] Department of Radiology, UHC "Mother Theresa", Tirana, Albania

Correspondence to:
Ilirjana Klironomi, MD, PICU, UHC "Mother Theresa", Tirana, Albania,
e-mail: ilirjanabakalli@yahoo.com

Primljeno/Received: 21. 5. 2013., Prihvaćeno/Accepted: 22. 11. 2013.

TABLE 1. Clinical, laboratory and radiological findings at admission

Nr	Pat. I.D.	Age (days)	Head CT scan	GCS (points)	Seizures	Vomiting	Fontanelle	Pupil	RBC *per* mm³	HgB g/dL	Platelet *per* mm³	Fibrinogen mg/dL	PT (in sec)	INR	Mechanical ventilation	Neuro surgery	Prognosis
1	A.H.	47	Subdural and diffuse intra-parenchymal hemorrhage	7	+	-	Bulging	N	2080 × 10^3	6.6	428 × 10^3	377	80	6.89	-	-	Very good
2	K.P.	32	Subdural and inter-hemispheric hemorrhage	7	+	+	N	N	1780 × 10^3	5.9	441 × 10^3	292	84	7.3	-	-	Neurologic sequels
3	T.F.	40	Subdural hematoma with significant midline shift	5	+	-	Bulging	Anisocoria	1754 × 10^3	5.8	364 × 10^3	374	89	7.84	+	+	Very good
4	I.S.	42	Diffuse intra-parenchymal hemorrhage	14	+	-	N	N	3400 × 10^3	10.4	420 × 10^3	310	79	6.79	-	-	Very good
5	M.J.	45	Intraventricular hemorrhage with hydrocephalus and cerebral edema	< 4	+	+	Bulging	Areactive bilateral mydriasis	1640 × 10^3	5.1	440 × 10^3	371	114	10.5	+	-	Exitus
6	S.L.	46	Infratentorial hemorrhage	< 4	+	+	Bulging	Areactive bilateral mydriasis	1890 × 10^3	5.4	307 × 10^3	360	98	**8.8**	+	-	Exitus
7	E.Ll.	45	Subdural hematoma	7	+	-	Bulging	N	1936 × 10^3	6.4	426 × 10^3	295	84	7.3	-	-	Very good

of the following was present: 1) platelet count normal or raised and normal fibrinogen; 2) prothrombin assay returned to normal after vitamin K administration; and 3) concentration of proteins induced by vitamin K absence (PIVKA) exceeded normal controls (according to the International Consensus definition for VKDB) (1).

In all cases, we evaluated clinical presentation, neurologic symptoms, time to diagnosis, coagulation data, imaging findings to evaluate the extent and site of hemorrhage (CT or MRI was performed in all infants), neurosurgical intervention, hospital course and neurodevelopmental outcome. Coma was evaluated according to the modified Glasgow Coma Scale (GCS) for infants and children.

RESULTS

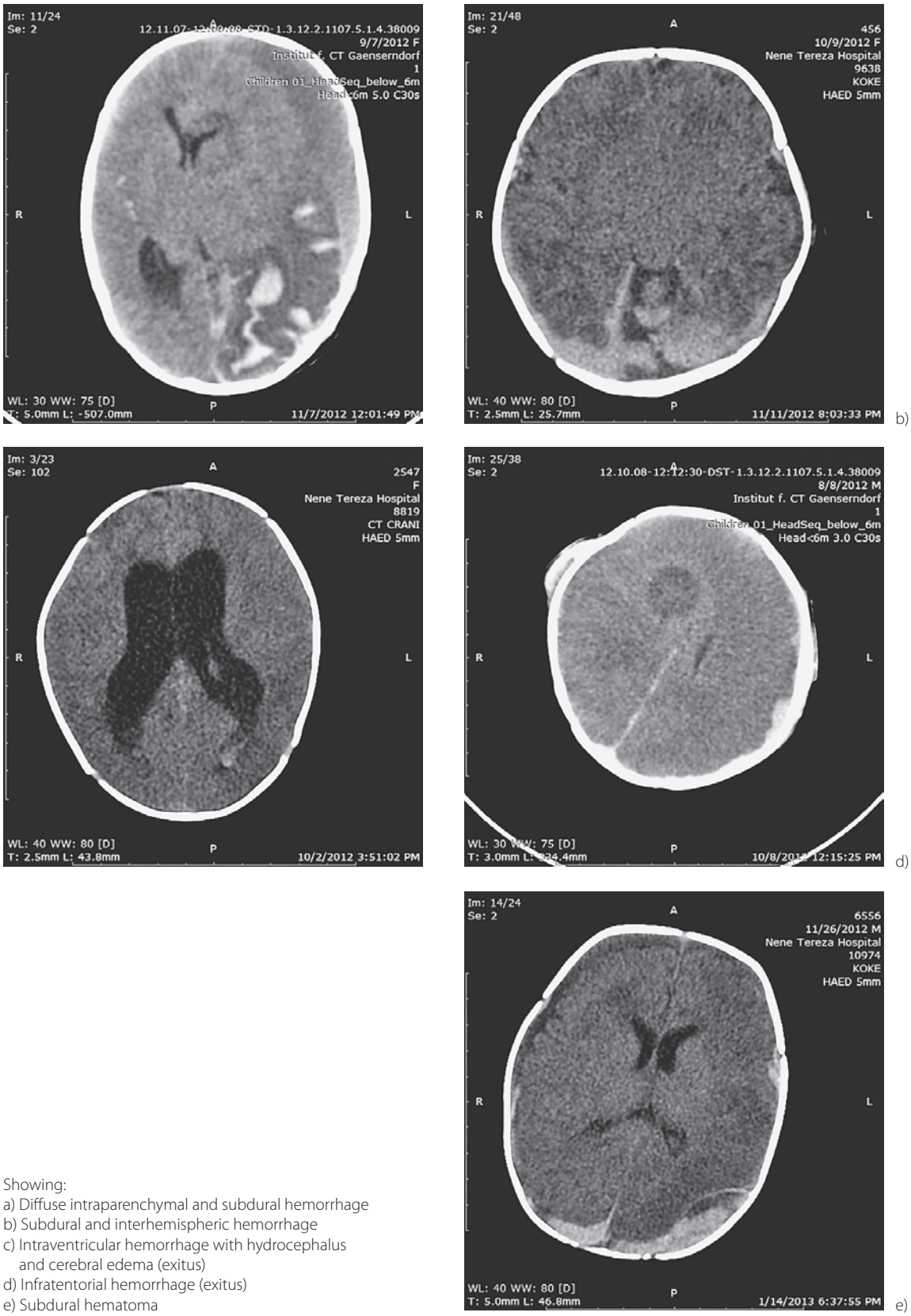
Seven infants were treated for ICH due to late VKDB during 2012 in Albania. All infants were born in hospital at term, meaning that prophylaxis with vitamin K 1 mg *i.m* was administered in the first hour of life (according to our Neonatology recommendation). The mean age at presentation was 41.8±4.9 days.

All cases were born at term, AGA (appropriate for gestational age), fully breastfed. The most frequent presenting complaints were seizures (100%) and vomiting (42.8%). The most frequent examination findings were coma (85.7%) and fontanelle bulging (71.4%), however, clinical presentation varied depending on the time of presentation in our hospital.

One of the patients had only one episode of seizure without fever one hour before admission in his medical history. After this episode, the clinical situation was stable, without neurologic deficits, able to breastfed, with normal fontanelle, slightly pale. During laboratory testing, a tendency to hemorrhage from the sites of puncture was observed, raising suspicion of ICH due to late VKDB. Laboratory tests confirmed a very prolonged PT. After the administration of 1 mg vitamin K intramuscularly (*i.m.*), clinical situation was stable and laboratory tests normalized within 24 hours.

In four cases, presentation included seizures, coma and severe anemia. Clinical suspicion enabled early diagnosis of VKDB in these infants and correct management. One of them presented with subdural hematoma and significant midline shift, and underwent neurosurgical surgery for evacuation of ICH. In all patients, clinical status improved in several days. Coagulation data normalized within 24 hours.

Another two cases with delayed diagnosis initially presented with vomiting. Their first presentation was in small cities of Albania. Their treatment in the first 24 hours consisted of



Showing:
a) Diffuse intraparenchymal and subdural hemorrhage
b) Subdural and interhemispheric hemorrhage
c) Intraventricular hemorrhage with hydrocephalus and cerebral edema (exitus)
d) Infratentorial hemorrhage (exitus)
e) Subdural hematoma

FIGURE 1. Radiologic findings in these infants with intracranial hemorrhage; computed tomography performed on day 1 of their admission to our Pediatric Intensive Care Unit revealed the following: (a) diffuse intraparenchymal and subdural hemorrhage; (b) subdural and interhemispheric hemorrhage; (c) intraventricular hemorrhage with hydrocephalus and cerebral edema (exitus); (d) infratentorial hemorrhage (exitus); and (e) subdural hematoma.

perfusion therapy (hypotonic liquids). Their clinical status aggravated first with seizures, and on admission to our hospital, they were in unresponsive coma. Based on CT in these two patients (intraventricular hemorrhage and infratentorial hemorrhage, respectively) and laboratory tests, we confirmed the VKDB and started the treatment immediately. Prognosis was poor and they both died.

Radiological findings varied, including subdural, intraparenchymal and intraventricular findings (Table 1).

Severe anemia requiring blood transfusion was present in six cases. Liver function was tested in all cases and results were normal. Before vitamin K administration, PT was very prolonged (89.7±12.5 s). Fibrinogen, Platelet count and C-reactive protein were normal in all cases. Treatment consisted in vitamin K *i.m.*, blood transfusion for the severe anemia (6 cases), mechanical ventilation (3 cases), and neurosurgery for evacuation of ICH in one patient. Within 24 hours, PT was normal in all cases.

The outcome was very good, without neurologic sequels in four (57%) cases. Persistent delay in mental development was recorded in only one case and lethal outcome in only two cases (Figure 1).

DISCUSSION

We report on patients with late hemorrhagic disease, i.e. on infants administered prophylactic vitamin K after birth and exclusively breastfed.

Late VKDB, primarily related to exclusive breastfeeding, is a coagulopathy that occurs in young infants due to inadequate plasma concentration of active coagulation factors II, VII, IX and X (5, 8). It usually occurs between the age of 2-12 weeks; however, it can be seen up to the age of 6 months (5, 6, 8).

Although placental transfer of vitamin K occurs, it is not adequate (9, 10), and that is why in the newborn plasma concentrations of these factors are normally 30%-60% of those in adults (7, 10). Numerous maternal medications during pregnancy that inhibit the action of vitamin K are associated with the early onset VKDB in the newborn.

On the other hand, vitamin K concentrations are physiologically low in breast milk, so that exclusively breast-fed infants are at an increased risk of vitamin K deficiency, as we found in all our cases reported.

In different parts of the world, various methods of vitamin K prophylaxis are practiced. In our country, the intramuscular prophylaxis is used, as in the USA, Australia, Canada and New Zealand. Oral prophylaxis is used in Switzerland, Germany, The Netherlands and Italy, and oral and parenteral prophylaxis in the United Kingdom (4, 7, 11, 12). According to reports from Asia and Europe, late VKDB has fallen from 4.4-7.2 cases *per* 100 000 births to 1.4-6.4 cases *per* 100 000 births upon the introduction of prophylactic regimens (6). Neither intramuscular nor oral vitamin K has been tested in randomized trials with respect to the effect on late VKDB (10).

Late vitamin K deficiency bleeding (2-12 wks after birth) appears to be reduced or prevented with parenteral administration of vitamin K at birth (6, 13, 14). Several studies confirm that *i.m.* vitamin K prophylaxis is safe and the treatment of choice for prevention of late VKDB and mostly all cases with hemorrhage had not received vitamin K prophylaxis (4, 9, 10, 13, 15, 16).

In contrast to these studies, *Solves* (17) and *Ciantelli* (18) in their case reports suggest that a potential risk is still present with a single dose of intramuscular vitamin K at birth. They conclude that 1 mg *i.m.* vitamin K at birth may be insufficient to prevent late VKDB. In their article, *Kasatkar et al*. (19) also report on 11 VKDB cases despite receiving appropriate dosage of parenteral vitamin K at birth. *Pirinccioglu et al*.(20) indicate that it may be questionable whether single dose vitamin K at birth is adequate for the prevention of late VKDB.

According to previous data, the incidence of late VKDB in Albania is 4-6 cases/100 000 live births. During 2012, we noted an increase in the incidence of primary late VKDB in Albania, presented with ICH ≈20/100 000 live births, even though according to our Neonatology recommendation, the prophylaxis with vitamin K 1 mg *i.m.* is administered in the first hour of life.

Is the higher incidence actually due to better diagnosis? Looking at the high incidence of late hemorrhagic disease in our country and in Turkey, we are inclined to speculate about some territorial factors, given the common parallel of Albania and Turkey, regardless of the surface of the country.

The incidence of intracranial hemorrhage from late VKDB is variable, showing significant geographical variation: the incidence in United Kingdom and Germany is >5 and 7.2 *per* 100 000 live births, whereas in Japan it is 20-25 *per* 100 000 live births, with fewer data from developing countries where this condition may be more common. In Thailand, the reported incidence is 35 *per* 100 000 live births (5, 13). Comparing with European countries, its incidence recorded in our country in 2012 was high.

Considering the increased incidence in our country, we agree with the opinions of *Kasatkar et al*. (19) and *Pirinccioglu et al*. (20) about vitamin K, that 1 mg *i.m.* vitamin K at birth prevents the classical form of hemorrhagic disease, but may be insufficient to prevent late VKDB.

Radiological findings in our cases were different from other studies (20, 21). The mortality rate of ICH from late VKDB remains high 10%-15% and at least 40% of the survivors have long term neurological sequels (5). It is still an important problem in Turkey resulting in a high mortality rate (31%-33%) and neurologic sequels in 36% of patients (21-23). In our study, the case fatality rate was 28.6% (2 cases) with neurologic sequels in 14% of cases. Analyzing these two cases, we identified two factors that led to mortality: 1) the infants with infratentorial ICH had a higher mortality rate (24); and 2) both these patients died, had delayed diagnosis, and their treatment with hypotonic liquids had aggravated their situation.

Considering the delayed diagnosis in these two cases, it is very important for all pediatricians to keep in mind that even with the correct prophylaxis, VKDB can still occur. They should be alert in case of a tendency to hemorrhage from the sites of puncture or signs of intracranial involvement, given that in more than 50% of cases, ICH is the presentation of VKDB.

CONCLUSION

Prophylaxis with 1 mg *i.m.* vitamin K at birth may be insufficient to prevent late VKDB. Pediatricians should keep in mind the possibility of VKDB in infants because early recognition and management are important to decrease the mortality.

NOVČANA POTPORA/*FUNDING*
Nema/*None*

ETIČKO ODOBRENJE/*ETHICAL APPROVAL*
Nije potrebno/*None*

DOPRINOSI AUTORA/*DECLARATION OF AUTHORSHIP*
Klironomi I. – prikupljanje podataka, pretraživanje literature, pisanje rada, kritički osvrt na rad/*data collection, literature search, writing paper, critical revision of the manuscript*
Sala D., Kito I., Gjeta I. – prikupljanje podataka/*data collection*
Celaj E. – pisanje rada/*writing paper*
Kola E., Lluka R., Celaj D., Sallabanda S. – kritički osvrt na rad/*critical revision of the manuscript*

SUKOB INTERESA/*CONFLICT OF INTEREST*
Autori su popunili *the Unified Competing Interest form na www.icmje.org/coi_disclosure.pdf (dostupno na zahtjev)* obrazac i izjavljuju: nemaju potporu niti jedne organizacije za objavljeni rad; nemaju financijsku potporu niti jedne organizacije koja bi mogla imati interes za objavu ovog rada u posljednje 3 godine; nemaju drugih veza ili aktivnosti koje bi mogle utjecati na objavljeni rad./*All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.*

REFERENCES

1. Sutor AH, von Kries R, Cornelissen EAM, McNinch AW, Andrew M. Vitamin K deficiency bleeding (VKDB) in infancy. On behalf of the ISTH Pediatric/Perinatal Subcommittee. Thromb Haemost. 1999;81:456-61.
2. Sutor AH. New aspects of Vitamin K prophylaxis. Semin thromb hemost. 2003;29:373-6. http://dx.doi.org/10.1055/s-2003-42680
3. Visser DY, Jansen NJ, Ijland MM, de Koning TJ, van Hasselt PM. Intracranial bleeding due to vitamin K deficiency: advantages of using a pediatric intensive care registry. Intensive Care Med. 2011;37:1014-20. http://dx.doi.org/10.1007/s00134-011-2175-7
4. No authors. Vitamin K – best prevention for newborns. Paediatr Child Health. 2002;7:588-9.
5. Danielsson N, Hoa DP, Thang NV, Vos T, Loughnan PM. Intracranial haemorrhage due to late onset vitamin K deficiency bleeding in Hnoi province, Vietnam. Arch Dis Child Fetal Neonatal Ed. 2004;89:546-50. http://dx.doi.org/10.1136/adc.2003.047837
6. Dharmendra J N, Sherman MP. Hemorrhagic disease of newborn. Available at: http://emedicine.medscape.com/article/974489-overview Updated: Apr 13, 2012.
7. Pichler E, Pichler L. The neonatal coagulation system and the vitamin K deficiency bleeding - a mini review. Wien Med Wochenschr. 2008;158:385-95. http://dx.doi.org/10.1007/s10354-008-0538-7
8. Gardner SL, Carter BS, Enzman-Hines M, Hernandez JA. Merenstein & Gardner's Handbook of Neonatal Intensive Care. 7th ed. St. Louis, Missouri: Mosby Elsevier; 2011;82:521-4.
9. Van Winckel M, De Bruyne R, Van De Velde S, Van Biervliet S. Vitamin K, an update for the paediatrician. Eur J Pediatr. 2009;168:127-34. http://dx.doi.org/10.1007/s00431-008-0856-1
10. Puckett RM, Offringa M. Prophylactic vitamin K for vitamin K deficiency bleeding in neonates. Available at: file:///F:/vit%20k/review.htm update: 06/08/2000.
11. Hasselt PM, Houwen RH, Dijk AT, de Koning TJ. Vitamin K deficiency bleeding in an infant despite adequate prophylaxis. Ned Tijdschr Geneeskd. 2003;147916:737-40.
12. Lippi G, Franchini M. Vitamin K in neonates: facts and myths. Blood Transfus. 2011;9:4-9.
13. American Academy of Pediatrics Committee on Fetus and Newborn. Controversies concerning vitamin K and the newborn. American Academy of Pediatrics Committee on Fetus and Newborn. Pediatrics. 2003;112:191-2.
14. McNinch A, Busfield A, Tripp J.Vitamin K deficiency bleeding in Great Britain and Ireland: British Paediatric Surveillance Unit Surveys, 1993 94 and 2001-02. Arch Dis Child. 2007;92:759-66. http://dx.doi.org/10.1136/adc.2006.104752
15. Hubbard D, Tobias JD. Intracerebral hemorrhage due to hemorrhagic disease of the newborn and failure to administer vitamin K at birth. South Med J. 2006;99:1216-20. http://dx.doi.org/10.1097/01.smj.0000233215.43967.69
16. Ipema HJ. Use of oral vitamin K for prevention of late vitamin k deficiency bleeding in neonates when injectable vitamin K is not available. Ann Pharmacother. 2012;46:879-83. http://dx.doi.org/10.1345/aph.1Q769
17. Solves P, Altés A, Ginovart G, Demestre J, Fontcuberta J. Late hemorrhagic disease of the newborn as a cause of intracerebral bleeding. Ann Hematol. 1997;75:65-6. http://dx.doi.org/10.1007/s002770050314
18. Ciantelli M, Bartalena L, Bernardini M, et al. Late vitamin K deficiency bleeding afterintramuscular prophylaxis at birth: a case report. J Perinatol. 2009;29:168-9. http://dx.doi.org/10.1038/jp.2008.131
19. Kasatkar P, Shetty S, Ghosh K. Dealyed vitamin K deficiency as a cause of bleeding: still a concern in the 21st century. Blood Coagul Fibrinolysis. 2010;21:608-10. http://dx.doi.org/10.1097/MBC.0b013e32833b645c
20. Pirinccioglu AG, Gurkan F, Bosnak M, Acemoglu H, Davutoglu M. Intracranial hemorrhage: clinical and demographic features of patients with late hemorrhagic disease. Pediatr Int. 2011;53:68-71. http://dx.doi.org/10.1111/j.1442-200X.2010.03199.x

21. Demirören K, Yavuz H, Cam L. Intracranial hemorrhage due to vitamin K deficiency after the newborn period. Pediatr Hematol Oncol. 2004;21:585-92. http://dx.doi.org/10.1080/08880010490500944
22. Yilmaz C, Yuca SA, Yilmaz N, Bektaş MS, Caksen H. Intracranial hemorrhage due to vitamin K deficiency in infants: a clinical study. Int J Neurosci. 2009;119:2250-6. http://dx.doi.org/10.3109/00207450903170437
23. Ozdemir MA, Karakukcu M, Per H, Unal E, Gumus H, Patiroglu T. Late-type vitamin K deficiency bleeding: experience from 120 patients. Childs Nerv Syst. 2012;28:247-51. http://dx.doi.org/10.1007/s00381-011-1575-x
24. Brouwer AJ, Groenendaal F, Koopman C, Nievelstein R A, Han SK, Vries LS. Intracranial hemorrhage in full-term newborns: a hospital-based cohort study. Neuroradiology. 2010; 52: 567-76. http://dx.doi.org/10.1007/s00234-010-0698-1

SAŽETAK

Intrakranijsko krvarenje uzrokovano kasnim nedostatkom vitamina K kod dojenčadi u Albaniji

Ilirjana Klironomi, Ermela Celaj, Elmira Kola, Robert Lluka, Durim Sala, Irena Kito, Durim Celaj, Inva Gjeta, Sashenka Sallabanda

Uz profilaksu vitaminom A pojavnost kasne bolesti krvarenja zbog nedostatka vitamina K (KNVK) se smanjila, ali je još uvijek moguća i u 50% slučajeva manifestira se intrakranijskim krvarenjem (IKK). Naglašavamo da profilaksa vitaminom K sprječava klasičan oblik hemoragijske bolesti i u manjoj mjeri sprječava kasnu KNVK. Cilj nam je poboljšati svjesnost o KNVK među svim pedijatrima. Analiziraju se podaci o sedmoro dojenčadi liječenih zbog IKK uzrokovane kasnom KNVK u Albaniji od siječnja do prosinca 2012. godine. Dijagnoza je postavljena prema međunarodno jednoglasno prihvaćenoj definiciji KNVK. Procjenjivali smo kliničke manifestacije, vrijeme do dijagnoze, koagulacijske podatke, bolnički tijek i ishod. Tijekom jednogodišnjeg razdoblja zabilježen je porast incidencije kasne KNVK u Albaniji, što se očitovalo stopom IKK od ≈20/100.000 živorođenih, čak i uz profilaksu od 1 mg vitamina K i.m. u prvom satu života. Najčešće manifestacije bile su konvulzije (100%) i povraćanje (42,8%). Najčešći nalazi pregleda bili su koma (85,7%) i izbočenje fontanele (71,4%). Radiološki nalazi su se razlikovali, a uključivali su subduralne (71,4%), parenhimne (14,3%) i intraventrikulske (14,3%) nalaze. Kirurška evakuacija IKK izvedena je samo u jednog bolesnika. Odgođena dijagnoza zabilježena je u dvoje (28,6%) bolesnika, oboje su umrli. U zaključku, profilaksa vitaminom K 1 mg i.m pri rođenju mogla bi biti nedovoljna za sprječavanje kasne KNVK. Pedijatri bi trebali voditi računa o mogućoj KNVK kod dojenčadi, jer su rano prepoznavanje i liječenje važni za snižavanje smrtnosti udružene s ovom bolešću.

Ključne riječi: vitamin K-nedostatak, terapija; intrakranijsko krvarenje