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Analysis of the Causes of Newborn Priapism: A Retrospective Clinical Study

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Abstract: Priapism is a rare condition in the newborn. The aim of this study was to investigate the demographic, etiologic and clinical features of neonatal priapism. We retrospectively analysed the data of 11 patients diagnosed with neonatal priapism in the neonatal intensive care unit between 2000 and 2019. Priapism was defined as an erection in the neonatal period, lasting more than 4 hours. Etiological examinations revealed polycythemia in one (9.09%) patient, D-dimer elevation in three patients, and heterozygous methyltetrahydrofolate 667 gene mutations in one patient. Other patients were considered idiopathic. Detumescence was achieved in all 11 (100%) patients during the follow-up period. The median hospitalization duration was 6 (IQR [4, 8]; range, 2–9) days. The median follow-up duration was 38 (IQR [30, 42]; range, 13–94) months for patients followed-up in our hospital after discharge. Neonatal priapism is a rare condition. Successful treatment results can be achieved with conservative methods. Data acquired from our study showed that diseases with a tendency to hypercoagulation belong to the etiology by damaging penile microcirculation and make the response to conservative treatment more challenging.

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Introduction

Priapism is a partial or complete penile erection lasting more than four hours without any sexual stimulus (Broderick et al., 2010). It can be divided into two groups: The low flow (ischemic or venous) and the high flow (non-ischemic or arterial). Ischemic priapism lasting more than four hours is a compartment syndrome requiring urgent treatment. Non-ischemic (high flow) priapism is a less common kind of priapism caused by irregular cavernous flow. Erection is painless and not completely rigid. Preservation of normal erectile function is the essential point in priapism management (Aktoz et al., 2011; Dust et al., 2011; Song and Moon, 2013). Although nearly 50% of all priapism cases are idiopathic, there are some specific known causes. Intracavernous treatment with papaverine, phentolamine, alprostadil or the combinations of these agents in adults is the most common cause of ischemic priapism (El-Bahnasawy et al., 2002).

Although the most common cause of low flow priapism is sickle cell anemia in children, in high flow priapism, trauma is the most common cause (Hekal and Meuleman, 2008). Priapism is a quite rare condition in neonates. Apart from idiopathic cases, the most frequently accused factor in the etiology of priapism, reported in the literature, is the increased blood viscosity in polycythemia (Walker and Casale, 1997; Meijer and Bakker, 2003). We thought that other factors that cause hyperviscosity in the neonatal period can be also involved in the etiology of priapism. Neonatal priapism cases are challenging for physicians due to a lack of experience and well-defined guidelines on this subject. Thus, the evaluation and management strategy remain uncertain. A limited number of case presentations are available on neonatal priapism in the literature. To the best our knowledge, we present the first original article written on this subject. The aim of our study was to extend our knowledge on the etiology of neonatal priapism and to suggest effective treatment methods.

Material and Methods

After obtaining consent from the local ethics committee (2018/229), patients who were diagnosed as having priapism in neonatal intensive care unit between 2000 and 2019 were investigated.

Patients having a duration of erection exceeding four hours in the newborn period were accepted as priapism and included in the study (Figures 1 and 2). Cases considered as transient physiological erection of the newborn that developed after the neonatal period were excluded from the study. Data on prenatal maternal history, maternal age, birth week, birth weight, delivery method, maternal medication, clinical characteristics, laboratory findings, radiological tests, treatment modalities and clinical management were evaluated. Penile blood gas analysis was performed in all cases. In addition, penile Doppler examination was performed by the radiology specialist in all cases.

Continuous data were reported as median with interquartile range (IQR). Clinical follow-up of the patients was carried out by the pediatricians and clinical management was carried out by the pediatricians and urologists together. Long-term follow-up was performed by the pediatricians.

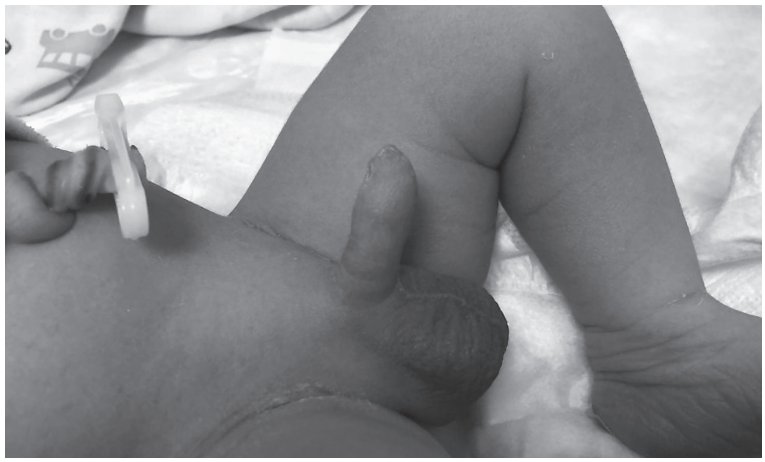

Figure 1 – A presentation of newborn priapism.

Figure 2 – A presentation of newborn priapism.

Results

In prenatal routine scannings, no evidence was found on blood group incompatibility. Two (18.1%) mothers had histories of smoking, two (18.1%) had bacterial vaginitis, one (9.1%) had folate deficiency, one (9.1%) had hypothyroidism and one (9.1%) had a history of preeclampsia. Apart from the mother who had thyroxine treatment due to hypothyroidism, none of the cases had a history of medication during pregnancy. Delivery was through spontaneous vaginal delivery in four (36.3%) and caesarean section in seven (63.6%) of the cases, and no complications occurred in any of the cases. Cesarian section was performed due to the demand of the mothers in two (18.1%)

Table 1 – Prenatal histories, characteristics of infants and mothers, etiological factors, laboratory findings and treatment methods

Case	Prenatal history	Maternal age	Birth week	Birth weight (g)	1. and 5. min APGAR	Infant's blood group	Maternal blood group	Htc	D-dimer elevation	Treatment
1	maternal smoking	26	38	3370	9-9	0 Rh+	0 Rh+	63	–	iv hydration
2	–	24	37	3390	9-10	0 Rh–	A Rh+	61	×	iv hydration
3	–	29	35	3060	9-9	A Rh+	B Rh+	58	–	iv hydration
4	preeclampsia	23	34	2890	7-8	AB Rh+	AB Rh+	74	–	iv hydration
5	–	17	38	3330	9-10	B Rh+	B Rh+	55	–	iv hydration
6	–	32	40	3230	8-9	A Rh+	A Rh+	58	×	iv hydration
7	–	28	42	3110	9-9	0 Rh–	0 Rh+	60	–	iv hydration
8	maternal smoking	29	38	3090	7-9	AB Rh+	B Rh+	61	–	iv hydration
9	MTHFR 667ct mutation	30	37	3860	8-8	AB Rh+	A Rh+	62	×	iv hydration
10	–	28	36	3040	8-9	B Rh–	AB Rh–	57	–	iv hydration
11	–	27	37	3390	9-9	B Rh–	B Rh–	56	–	iv hydration

Htc – hematocrit; iv – intravenous; MTHFR – methylenetetrahydrofolate reductase

cases, preeclampsia in one (9.0%), cephalopelvic disproportion in two (18.1%) and history of multiple caesareans in two (18.1%) cases. Median maternal age was 28 (IQR [24, 29]; range, 17–32) and median birth week was 37 (IQR [36, 38]; range, 34–42). Median birth weight was observed as 3,230 g (IQR [3060, 3390]; range, 2890–3860) (Table 1).

In the first physical examination, one of the patients had a one sided undescended testicle. The physical examinations were normal for other patients. Urine output and post-void residual volume were normal in all patients. One (9.09%) patient had polycythemia based on the etiologic examinations (Htc – hematocrit > 65). It was found that in this case preeclampsia developed during pregnancy and delivery was performed by cesarian section. D-dimer positivity was detected in three patients (27.2%), and it was observed that in one of three cases, heterozygote methylenetetrahydrofolate reductase (MTHFR) 667ct gene mutation positivity was detected in the mother before delivery. While hyperhomocysteinemia was observed in one of the patients, but the homocysteine level was normal in the others. No abnormal findings were observed in the other organ systems of these patients. Apart from these, no etiologic factors were found through imaging methods and laboratory findings in seven (63.6%) patients and these cases were regarded as idiopathic.

The median time to observe priapism was 3 days (IQR [3, 7]; range, 1–9). Median duration of episode was 3 days (IQR [3, 4]; range, 1–7). In this priapism cases, there were no stuttering priapism. No penile blood gas examination was found in favour of ischemic priapism. Normal arterial and venous flow was detected in all cases in colour Doppler ultrasonography. Detumescence was provided in all of the patients (100%) after 50 cc/kg/day fluid treatment and follow-up (Table 1). Median hospitalization duration was 6 days (IQR [4, 8]; range, 2–9). Median follow-up duration was 38 months (IQR [30, 42]; range, 13–94) for the patients in our hospital after discharge. No recurrent priapism attacks were detected in the patients during follow-up.

Discussion

Neonatal priapism is a rare case with only 18 cases reported since 1876 in the literature. The real incidence of neonatal priapism is unknown, but Merlob and Livne (1989) found the incidence as 0.15 in 1,000 live births between 1974 and 1988 in their center in a small surveillance study. In neonatal males, erection generally occurs through the slightest tactile simulation, and may often be stimulated by a completely full bladder. Typically, these physiological erections last a few minutes and quickly ends after the stimulus disappears (Burgu et al., 2007). Merlob and Livne (1989) stated that the term neonatal priapism was not suitable, and it would be more appropriate to call it as prolonged neonatal penile erection.

The etiology of priapism differs significantly among patient populations, but blood dyscrasias, pharmacotherapy, neurologic conditions, malignancy, and trauma are among common identifiable causes. Sickle cell disease constitutes nearly 70% of pediatric priapism but does not occur in the neonatal period due to the fetal

hemoglobin dominance (Mishra et al., 2020). Although neonatal priapism is most commonly idiopathic, polycythemia is the most common cause among its identifiable etiologies. The most important factor here is hyperviscosity and the resultant slowing of microcirculation. This situation results in decreased penile venous outflow and permanence of penile erection. Four of 18 neonatal priapism cases reported to date were related to polycythemia (Humbert et al., 1969; Merlob and Livne, 1989; Dust et al., 2011). Although penile blood gas examination was not performed, a non-ischemic course of priapism was seen in these cases.

In our study, the cause was observed to be polycythemia in one patient (9.09%) which is a lower ratio to the cases in the literature. In that patient, the mechanism underlying polycythemia was considered as preeclampsia during pregnancy. When etiologic factors other than polycythemia in the literature are considered, it was observed that one case had recurrent blood transfusions and hypoxia, one case was secondary to congenital syphilis, one case had central nervous system trauma secondary to forceps use and another case was secondary to bilateral spontaneous pyocavernositis (Larocque and Cosgrove, 1974; Amlie et al., 1977; Sood et al., 2006). The etiology of the cases could not be determined in the remaining nine cases, which were regarded as idiopathic. Different from the cases in literature, the cause of the priapism was considered to be secondary to microthrombosis in penile microcirculation in three patients in our study, and the thrombosis in one of these was related to heterozygote MTHFR 667ct gene mutation positivity.

MTHFR is an important enzyme in folate metabolism and is formed by 656 aminoacids (Homberger et al., 2000; Rosenblatt, 2001). A mutation occurring in MTHFR gene (C677T polymorphism is the most common) lowers enzyme activity. Levels of 5-methyltetrahydrofolate (MTHF) decreases, and the amount of 5, 10-MTHF and plasma homocysteine levels increases as the result of decreased MTHFR activity (Peng et al., 2001). Due to the hypomethylation and acylation effect of sulfhydryl group of homocysteine, homocysteine is known to cause harmful effects on vascular endothelium (Födinger et al., 2000). It was stated that homocysteine increased platelet consumption due to this resultant vascular damage and thus caused thrombosis (Donnelly and Rock, 1999).

Clinically, D-dimer is most commonly used for venous thromboemboli and disseminated intravascular coagulation diagnosis and follow-up (Righini et al., 2008; Wada et al., 2014). Apart from these, D-dimer also increases due to thromboses formed in other regions inside the body (Taylor et al., 2001). Including the one heterozygote MTHFR 667ct gene mutation positive case, plasma D-dimer levels were detected high in three cases in our study. Even though verifiable thromboses were not detected in all three cases in Doppler examinations, it was considered that D-dimer levels could have increased secondary to a thrombosis that was present in the penile venous microcirculation but could not be detected in imaging.

Although the starting time was generally reported as the first or second day of life in the priapism cases presented in literature, it was reported as the 37th day in one case

(Amlie et al., 1977). Priapism duration is quite variable, but the mean was reported as 4–5 (range 2–12) days. In our study, the median priapism starting time was reported as 3 (IQR [3, 7]; range, 1–9) days after birth, the median duration of the episodes 3 (IQR [3, 4]; range, 1–7) days and the median duration of hospitalization duration as 6 (IQR [4, 8]; range, 2–9) days.

When the management of priapism detected in the neonatal period was examined, it was reported that detumescence was provided through follow-up in 75% of the cases in literature, and two cases related to polycythemia were in this group (Humbert et al., 1969; Larocque and Cosgrove, 1974; Walker and Casale, 1977). In two other cases for which the etiological factor was polycythemia, detumescence was not provided through follow-up, and in one case it was provided through phlebotomy and through exchange transfusion in another (Humbert et al., 1969; Walker and Casale, 1977). Detumescence was provided immediately after intravenous (iv) ketamine infusion in one of the idiopathic cases (Stothers and Ritchie, 1992). Contrary to the ratio of the cases in literature, detumescence was provided after follow-up and iv fluid administration in all of 11 cases (100%) in our study. On the other hand, polycythemia is the common etiological factor in resistant cases in the literature and only one patient had polycythemia in our cohort. We think that this is the origin of our different results to those in the literature.

According to literature data, the follow-up was unfortunately limited to early infancy and the longest follow-up duration was 8 years (Merlob and Livne, 1989). The median follow-up duration of the patients was 38 (IQR [30, 42]; range, 13–94) months in our study, and the longest follow-up was 94 months; no priapism recurrence was detected in any of the patients.

Erectile dysfunction is a problem that should be considered in priapism cases occurring in childhood and adulthood. The connection of priapism with erectile dysfunction risk cannot be presented clearly because neonatal priapism cases presented in the literature are rare and there were no long-term follow-ups. In the case presentation of Sood et al. (2006), it was stated that long-term neonatal priapism could cause severe complications such as pyocavernositis.

Apart from the neonatal physiologic erection, a careful evaluation should be performed for polycythemia, neurologic conditions, and urinary tract obstruction in priapism cases. Starting from high D-dimer levels and the MTHFR mutation in some patients, our study showed that hypercoagulation was among the risk factors that should be considered in the etiology of priapism. The arterial blood flow of patients should be evaluated through penile Doppler ultrasonography and also pediatric urologists should evaluate penile blood gas analysis. As in all cases, penile blood gas and penile Doppler ultrasonography showed high flow priapism in our cases. These findings support “neonatal priapism is highly non-ischemic” theory in the literature. Rather than an aggressive intervention, observation alone is enough in these cases in the first stage (Merlob and Livne, 1989; Dust et al., 2011). Even though penile Doppler ultrasonography findings do not take us to venous return disorder in patients with priapism without regression through follow-

up, it should be kept in mind that polycythemia or other diseases creating a tendency to hypercoagulation may contribute to priapism occurrence by harming penile venous microcirculation and make the response to conservative treatments challenging.

Although the current study reported new findings, it had several limitations. First, the study was performed in a retrospective manner and had a small patient population. In this study, data related to the results and controls were collected by retrospective table review of the patients followed-up in the pediatric clinic. This could have introduced collection bias in the results.

Conclusion

Although no etiologic factor other than polycythemia could be presented in literature, data acquired from our study showed that diseases producing a tendency to hypercoagulation could be included in the etiology of priapism by damaging penile microcirculation and makeing the response to conservative treatment challenging.

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