

Dept. of Animal Hygiene & Nutrition,  
Fac. Vet. Med., Assiut Univ., Assiut, Egypt.

**NEONATAL HYDROCEPHALUS IN RABBITS  
AT ASSIUT GOVERNORATE**  
(With 3 Tables and 15 Figures)

By

**H.A. ABDEL-RAHEEM; A.N. SAYED;  
R.S. IBRAHIM\* and M. MUBARAK\*\***

\*Dept. of Poultry Diseases, \*\* Dept. of Pathology,  
Fac. Vet. Med., Assiut Univ., Assiut, Egypt.

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الحدوث الطبيعي لتضخم الرأس المائي في الأرانب الوليدة بمحافظة أسيوط

حسن عباس عبدالرحيم ، عبد الباسط نصر سيد ،  
رجب سيد إبراهيم ، محمد مبارك

أظهرت هذه الدراسة زيادة حدوث الأصابات في النجاس ومعدل منخفض للأجهاض في ثلاث مستعمرات من الأرانب في محافظة أسيوط . حدثت هذه المشكلة في نهاية فصل الصيف وخصوصا في شهر أكتوبر من عام ١٩٩٩م. أظهرت الولادات أو النجاس حدوث تضخم الرأس المائي مع درجات مختلفة من جحوظ العيون وعتامة القرنية وحتى العمى الكلي. عند تحليل مستوى المصل من فيتامين (أ) في الأمهات والنجاس تراوح المعدل من ٤٤١ إلى ٢١٣٢ ميكروجرام لكل ١٠٠ مللي في الأمهات بأقل من المعدل الضابط (٥٨٢٧ ميكروجرام لكل ١٠٠ مللي) بينما في النجاس تراوح بين ٢٩٧٨ إلى ٣٥٤٢ ميكروجرام لكل ١٠٠ مللي بأقل من المعدل الضابط (٦٣٤٩ ميكروجرام لكل ١٠٠ مللي). وقد وجدت علاقة طردية بين انخفاض مستوى فيتامين (أ) في المصل للأمهات وشدة حدوث الإصابة في الولادات الناتجة . كانت النتائج سلبية بالنسبة لمحاولة العزل البكتيري وكذلك بالنسبة للإصابة بالكوكسيديا الأوروية والكبدية. أظهر الفحص الباثولوجي تغيرات واضحة في أنسجة المخ للأرانب المصابة. عند التدخل بالعلاج باستخدام محلول مائي من فيتامين أ د هـ عن طريق الحقن وماء الشرب للأمهات كانت النتائج مرضيه تماما حيث اضمحلت هذه الإصابة في الولادات التالية.

**SUMMARY**

A total number of 42 does from three rabbit colonies in a farm at El-Hawatka district (Assiut governorate) were experimented on. The does had a history of stillbirth, low incidence of abortion and neonatal

affections manifested in hydrocephalus, variable degrees of xerophthalmia, corneal opacity and even blindness. The problem exaggerated in the late summer and reached its peak in October, 1999. Level of vit.A in ration was lower than the normal requirement of rabbits, its content was 3800 IU/ Kg. Serum vit.A levels in both does (4.41 - 21.32 ug/ 100 ml) and growing rabbits (29.78 - 35.42 ug/ 100 ml) were lower compared with control (58.27 ug/100 ml in mother does and 63.49 ug/100 ml in growing rabbits). There was proportional relationship between serum vit.A of mother does and the severity of affection in the neonates. The sacrificed neonates were proved to be free from bacterial infection as well as cecal and hepatic coccidiosis. Histological examination revealed significant encephalopathological changes which encompassed gray and white matters. Microscopically, aqueduct of Sylvius was patent and no obstruction site was detected in the brain tissue. Parental and oral treatment of mother does using vit. AD<sub>3</sub>E restored the condition in all colonies with disappearance of deficiency signs in most neonates in subsequent litters.

*Key words: Rabbit- Hydrocephalus- Vit.A deficiency.*

## INTRODUCTION

One of the most important problems of concern in rabbit production is vit.A deficiency. The relevant manifestations are infertility and different neonatal pathological affections including hydrocephalus (Cheeke, 1987). The typical reproductive effects of vit. A deficiency in rabbits are; low conception rate, fetal resorption and small weak litters (Cheeke, 1994). The first order of diagnosis is determination of vit. A level in liver or blood.

Hydrocephalus is a form of edema in the central nervous system and refers to the slow accumulation of excess cerebrospinal fluid (CSF) within the ventricular system (internal hydrocephalus) or within the subarachnoid spaces (external hydrocephalus) (Runnels *et al.*, 1965; Jubb and Huxtable, 1993; Storts, 1995; Summers *et al.*, 1995; Jones and Koestner, 1997). Also, there are two main types of hydrocephalus, namely acquired and congenital types (Leech *et al.*, 1970; Leipold *et al.*, 1971; Greene *et al.*, 1974; D,Amato *et al.*, 1986; Jubb and Huxtable, 1993).

Hydrocephalus was reported as an inherited condition or congenital deformity among newborn rabbits (Lieve, 1988). Hydrocephalus may develop within few weeks in young rabbits born to marginally vit.A-deficient does (Woolam and Millen, 1955 and Millen and Woolam, 1956). Also, decreased breeding efficiency, early fetal deaths, abortion and congenital neonatal malformations, including hydrocephalus, were reported in rabbit colonies suffering from vit. A deficiency (Greene, 1965; Harrington and Newberne, 1970 and Check, 1987). Moreover, Harrington and Newberne (1970) presented an experimental evidence that vit.A deficiency in pregnant does can lead to hydrocephalus in newborns.

The present work was directed for investigation of a field problem in 3 rabbit colonies where stillbirth and neonatal hydrocephalus were recorded. Therefore, we hypothesized that, vit.A status of the animals in the relevant colonies had influenced the incidence and severity of hydrocephalus. The present study was designed to test this hypothesis by examining the affected cases before and after vit.A supplementation.

## **MATERIALS and METHODS**

### **Rabbits:**

Three colonies of New Zealand rabbits designated as; A (20 does), B (7 does) and C (15 does) at El-Hawatka district (Assiut governorate) suffered from stillbirth and neonatal affections including hydrocephalus as shown in Table (1) were chosen for the study. Rabbits were raised in batteries and fed on rations from the same source.

Clinical examination of signs and lesions manifested by the breeding rabbits and surviving youngs was done and recorded. Additional age-matched 10 animals from the same farm (5 mother does and 5 young rabbits) served as a control group.

### **Feeding:**

This field problem occurred in late summer with the incidence peak in October, 1999. Due to absence of green berseem, rabbits were fed on pelleted commercial diet which supplied about 2.9 Mcal/kg digestible energy (DE) and 17.0 % crude protein. The physical composition of pelleted commercial diet is shown in Table (2).

**Table 1:** Frequency of stillbirth and neonatal affections in different rabbit colonies

Colony	Abortion Rate	Stillbirth	Affected neonates	Affection
Colony A	3 / 20	17 / 20	121 / 135	Hydrocephalus and blindness
Colony B	-	7 / 7	31 / 40	Hydrocephalus and xerophthalmia
Colony C	-	3 / 15	19 / 75	Slight hydrocephalus and corneal opacity

**Table 2:** Physical composition of pelleted commercial rabbit ration

Ingredient	Composition (%)
Corn, ground	40.0
Wheat bran	24.5
Soyabean oil meal	16.0
Berseem hay meal	15.0
Molasses	3.0
Dicalcium phosphate	1.0
Common salt	0.5
<b>Total</b>	<b>100</b>

**Determination of vit.A in ration:**

Pooled ration sample (500 g amount) was dried, ground and thoroughly mixed and then prepared for vit.A determination according to the official method of analysis of A.O.A.C. (1984).

**Determination of vit.A in serum:**

Blood samples were obtained from both mother does and surviving young rabbits. Vit.A in harvested sera of affected and control animals was estimated according to the method of Carr and Price (1926). 2 ml of the harvested blood serum was pipetted into sterile test tubes and then 2 ml of absolute alcohol (96%) was run slowly from the pipette and the mixture was shaken well. 5 ml of petroleum ether was added to the mixture which was shaken vigorously for 15-20 minutes on a mechanical shaker, then removed and left till the contents settled down. The clear supernatant fluid containing the dissolved vit.A was transferred to clean dry test tube. For estimation of vit.A, all test tubes

were immersed in water bath at 50-60°C to evaporate petroleum ether. The residue in each test tube was dissolved in 0.2 ml chloroform and then one drop of acetic acid anhydride and 2 ml of antimony trichloride dissolved in chloroform were added. The spectrophotometer was adjusted at 620 nm wave length and measured against chloroform as a blank. Blood serum vit. A was expressed as ug / 100 ml.

**Bacteriological and parasitological examinations:**

Bacterial isolation was tried from brain, liver and eye tissues of affected growing rabbits by cultivation on dextrose starch agar (DSA, Difco) and blood agar plates at 37°C for 48 hours. For parasitological examination, cecal contents and cecal mucosal scrapings were examined microscopically for the presence of coccidial oocysts. Moreover, liver crushed smears and gall bladder smears were examined.

**Vit. A treatment:**

Treatment of does was carried out using injectable vit. A in the form of vitamin AD<sub>3</sub>E. Each rabbit received 25.000 IU in a single dose. Moreover, water soluble vit. AD<sub>3</sub>E was added to the drinking water for 7 days.

**Gross pathology:**

Immediately after sacrifice of the affected young rabbits, routine post-mortem examination was conducted. Skull bones of the hydrocephalic rabbits were examined thoroughly for their state of ossification. Cranial bones were then removed to examine the cranial cavity and brain tissue.

**Histopathology:**

Representative samples were taken from the brain tissues and also from other organs, including liver, heart, lungs, kidneys and spleen as well as other tissues. Tissue samples were fixed in 10% neutral-buffered formalin and then processed routinely for paraffin embedding technique. Embedded tissues were sectioned at 3 u and stained with haematoxylin and eosin (HE) (Bancroft and Stevens, 1982).

**Statistical analysis:**

All data concerning serum vit.A levels were subjected to one-way analysis of variance (ANOVA) and individual differences ( $P < 0.05$ ) among colonies were determined by use of Duncan's multiple range method (1985).

## RESULTS

### Clinical picture:

#### Farm A:

Out of 135 neonates given by twenty mother does, 121 cases manifested hydrocephalus and blindness. Abortion occurred in 3 out of 20 mother does. The surviving growing rabbits showed hydrocephalus with pulging of the head dorsally as well as xerophthalmia and blindness. Poor body condition and musculature were noticed in growing rabbits aged 1-2 weeks.

#### Farm B:

All does (100 % frequency) gave stillbirths and neonatal affections. The growing survivors showed hydrocephalus and xerophthalmia.

#### Farm C:

There was early appearance of neonatal affections in the offsprings of 3 out of 15 mother does. The neonates suffered from mild degrees of hydrocephalus and corneal opacity

#### Vit.A content in ration:

The level of vit.A in the ration of rabbits was 3800 IU/ kg.

#### Serum analysis:

The mean values for serum vit.A of affected does, growing rabbits and control animals are presented in Table (3).

Table 3: The mean values of serum vit.A (ug/100ml) in affected and control rabbits in different colonies

Rabbit	Number sampled	Average serum vit.A in does (ug/100 ml)	Average serum vit.A in youngs (ug/100 ml)
Colony A	10*	5.23 ± 0.50 <sup>c**</sup>	29.78 ± 2.05 <sup>c</sup>
Colony B	10	4.41 ± 0.41 <sup>c</sup>	31.05 ± 1.95 <sup>bc</sup>
Colony C	10	21.32 ± 1.04 <sup>b</sup>	35.42 ± 1.46 <sup>b</sup>
Control	10	58.27 ± 1.97 <sup>a</sup>	63.49 ± 3.39 <sup>a</sup>

\*Number of sampled animals = 4 does and 6 growing rabbits in each colony.

\*\* Figures in the same column having the same superscripts are not significantly different (P<0.05).

**Bacteriological and parasitological examinations:**

There was no any bacterial species recovered from tissues of sacrificed rabbits. Moreover, all examined cases were negative for cecal and hepatic coccidiosis.

**Vit.A treatment:**

The treated young rabbits or mother does responded positively especially after correction and addition of vit. AD<sub>3</sub>E to their drinking water. Only 7 out of 120 offsprings were still affected in colony A, while no more cases recorded in colonies B and C.

**Pathological findings:**

**Gross pathology:**

The surviving neonates at 1-2 weeks of age manifested hydrocephalus. Skulls of the affected animals were obviously enlarged (Fig. 1). Skull bones were dommed dorsally (Fig.2 a&b) (prominent bulging of the dorsal portion of the head). Cranial bones were found poorly ossified, and their fusion on the dorsal midline and laterally was obviously lacked. Temporal, frontal and parietal bones were markedly thinned and the sutures between them were ununited. These bones were only separated by fibrous membranes. The anterior fontanelles were soft. Unossified clavial tissue was also noticed at the occipital area. Base of the cranium was flattened. After reflection of the enlarged unossified cranial bones, straw -yellow fluid was seen accumulated in the cranial cavity (Fig. 3) Cerebral hemispheres after removal of the cranial bones were found friable and collapsed (Fig. 4 a&b). Cerebellum was compressed and displaced caudally. On incision, the cerebral parenchyma was limited to a thin tissue layer enclosing the accumulated fluid in the lateral ventricles (Fig. 5). Xerophthalmia and varying degrees of corneal opacity were observed in the hydrocephalic cases. No gross abnormalities were observed in other organs and tissues.

**Histopathology:**

Using low power magnification, the dilation of the lateral ventricles was marked. Lateral ventricles were also extended into the frontal lobe on the expense of the neuropil which was apparently atrophied. The atrophic changes of white matter were more pronounced than that of gray matter. The atrophying process also involved corpus callosum. At the surface, the meningeal blood vessels were dilated and edema obviously separated the meningeal membranes (Fig. 6).

Yellowish-brown spots were observed at the meningeal surface (Fig. 7) and also on the inner surface of the compressed neopallium. Multiple diverticula were seen extending into the compressed white matter which showed clefting at the diverticular sites. No ependymal lining was detected at these diverticula. At other sites of the ventricular lining, the ependymal cells were hyperplastic (forming folds) (Fig. 8). Remarkable subependymal gliosis was noticed (Fig. 9). Perivascular and pericellular edema and swollen axons were frequent in the gray matter (Fig. 10). Considerable number of neurons were swollen and others were shrunken. Vacuolated foamy glia cells were observed. Chromatolysis was noticed in neuronal cells (Fig. 11). White matter was edematous and its glial elements were decreased in number. Spongy status, due to demyelinating process, was observed in the brain stem (Fig. 12). Purkinje cell layer in the cerebellum was obviously distorted (Fig. 13). Aqueduct of Sylvius was patent (Fig. 14). However, at the level of brain stem pronounced periductal gliosis was seen (Fig. 15). Eye lesions were represented by degeneration (cell swelling) of corneal epithelial cells and marked edema of the corneal stroma. Focal keratinization of the corneal epithelium was also found.

#### DISCUSSION

Both vit.A deficiency and toxicity adversely affect female production in terms of low conception rates, fetal resorption, abortion, low neonatal survival and hydrocephalus in neonates (Check, 1987). In the present work, three New Zealand rabbit colonies manifested similar clinical picture and lesions. Female rabbits sometimes gave abortion, stillbirth and neonatal deaths. Neonates were frequently normal at birth but after 1-2 weeks showed variable degrees of hydrocephalus, blindness and weak body. As in other species, infertility and reproductive failure due to vit.A deficiency are expected in does (Lamming *et al.*, 1954a). Harrington and Newberne (1970) reported decreased breeding efficiency, early fetal deaths, abortion and congenitally malformed youngs in rabbit colonies suffering from vit.A deficiency. Abortion and low fertility due to vit.A deficiency, as observed in these cases, indicate that vit.A is required for maintenance of pregnancy (Payne *et al.*, 1972). In accordance with our results, Millen and Woollam (1956) described that young rabbits born to asymptomatic marginally vit.A-deficient females may appear normal at birth but may develop hydrocephalus and other signs of deficiency within few weeks postpartum. However, the



occurrence of hydrocephalus is related to the maintenance of does on deficient diet prior to breeding. The incidence of hydrocephalus in different colonies and in litters within a single colony varied. This may be due to the possibility of differences in maternal vit.A stores and thus the rate of depletion of individual animals (Harrington and Newberne, 1970).

The level of vit.A in the diet of rabbits was 3800 IU/kg which is lower than the requirement of rabbits for vit.A (10000 IU/Kg) as reported by Lebas (1980) while Payne et al. (1972) found that 1160 IU/Kg diet was not adequate for does in production. The mean values for serum vit.A in both does and newborns in all studied colonies were significantly lower ( $p < 0.05$ ) than that of the control rabbits. The average serum vit.A values (ug /100 ml) in does from colony A ( $5.23 \pm 0.50$ ) and colony B ( $4.41 \pm 0.41$ ) were significantly lower ( $P < 0.05$ ) than that in colony C ( $21.32 \pm 1.04$ ) and this was reflected on the severity of clinical signs in colonies A and B. The level in colony C ( $21.32 \pm 1.04$ ) was significantly lower ( $P < 0.05$ ) than control ( $58.27 \pm 1.97$ ). For growing or newborns, the mean values of serum vit.A in colony A ( $29.78 \pm 2.05$ ) were significantly lower ( $P < 0.05$ ) than that in colony C ( $35.42 \pm 1.46$ ) and nearly similar with colony B ( $31.50 \pm 1.95$ ). The normal level of vit. A in the blood plasma of most animals ranges between 20-60 ug/100 ml, while normal level in rabbit may be somewhat higher. Lorente and Miller (1977) reported a value of 80 ug of retinol/100 ml. The critical serum concentration below which a significant incidence of hydrocephalus was found to range between 20 and 30 ug / 100 ml serum (Harrington and Newberne, 1970). The same authors stated that in case of maternal level below 20 ug/100 ml at conception, the youngs in 70% of the litters were hydrocephalic at birth, while youngs born from does with serum level above 40 ug/100 ml generally had no gross hydrocephalus at birth. The present results indicated serum level of vit.A in does ranging from 4.41 to 21.32 ug/100 ml while in youngs it ranged from 29.78 to 35.42 ug/100 ml.

Positive response of all mother does to vit.A treatment in this work confirmed that was explained by Millen and Dicksan (1957) who stated that administration of vit.A to deficient rabbits results in a rapid decline in cerebrospinal fluid pressure until reaches normal level. The dose response, relative to the normal level of the rabbits under conditions of vit.A sufficiency, would serve as an indicator of poor vit.A status of

these animals. Harrington (1969) found that eye lesions occur in both adult and young animals at few weeks of age and unless vit.A therapy is instituted at this stage, the condition advances to permanent blindness. Eye lesions observed in the present cases were the result of prolonged vit. A deficiency which can produce permanent blindness due to corneal keratinization (Harrington and Hunt, 1974).

From the pathological viewpoint, in the congenital type of hydrocephalus failure of ossification and fusion of the cranial bones gives the chance for the expansion of the cranial cavity, as demonstrated in the present cases, by the accumulated CSF (Summers *et al.*, 1995). The present cases showed communicating type of hydrocephalus where the excess CSF was found in the cranial cavity and within the brain ventricles. This hydrocephalus type is the usual one in newborns (Jone and Koestner, 1997). Compression of the brain tissue by the accumulated CSF can result in this type through mechanical interference with the ventricular circulation. The presently described encephalopathological changes were undoubtedly the result of mechanical damage exerted by the accumulated CSF. The observed yellowish brown spots at the meningeal surface and at the inner surface of neopallium were probably the result of previous haemorrhages. This indicates the low resistance of brain tissue for mechanical damage. However, some of the noticed histological changes can be ascribed to circulatory disturbances including compromised vascular perfusion of neuronal cells (Del Bigio, 1993). No intracranial obstruction sites or stenotic aqueductal malformations could be detected in our cases. This conforms with the previous histological observations on congenital hydrocephalus that the inducing factors are usually obscure (Jubb and Huxtable, 1993). In absence of aqueductal insufficiency, the probability of under-absorption of CSF was usually suggested (Calhoun *et al.*, 1962). Suspicion of nutritional deficiencies has been usually arisen in cases of newborn hydrocephalus which can't be explained on a hereditary basis (Lindsey and Fox, 1994). Basing on the histopathological examination of the present hydrocephalic cases, the suspicion of some sort of nutritional deficiencies in feed of the breeders was more approved since the studied cases were born hydrocephalic. The obtained data indicated vit.A deficiency in the breeders' feed and a state of hypovitaminosis A in the sera of breeders and hydrocephalic newborns. Vit.A is known to be essential for epithelial growth and integrity (Austic and Scott, 1997). It is most probably that vit.A deficiency in our cases caused damage of the

arachnoid villar epithelium. The latter is the site of venous resorption of CSF where the arachnoid villi form in the walls of the meningeal veins (Summers *et al.*, 1995). Undoubtedly, damage of the arachnoid villar epithelium leads to accumulation of CSF due to discrepancy between production and resorption of CSF. Also, impairment of the resorptive ability of the arachnoid villar epithelium was reported as a contributor (Fiays *et al.*, 1968 and Eaton, 1969).

As far as we aware there is no published report in Egypt on neonatal hydrocephalus in rabbits which could be attributed to vit.A deficiency. This study presented hydrocephalic newborn rabbits which could be ascribed to a state of vit.A deficiency. The feed of the breeder animals was deficient in vit.A and analysis of sera obtained from newborns and breeders revealed hypovitaminosis A. In the view of the present results, the vitamin status of the breeders and dietary vitamin levels should be investigated when there are hydrocephalic cases among newborn rabbits.

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### LEGENDS FOR FIGURES

- Fig. 1:** Two-week-old rabbit (colony A) showing hydrocephalus. The skull is markedly enlarged. The affected animal is depressed.
- Fig. 2:** (a) Lateral view of skull of a hydrocephalic rabbit. Note the dorsal doming of the skull bones and protrusion of the eye ball (xerophthalmia). (b) Anterio-dorsal view of skull of a hydrocephalic rabbit. Note the doming of cranial bones.
- Fig. 3:** Cranial bones were reflected laterally to reveal the intra-cranial accumulation of CSF and the collapse of cerebral tissue. 2-week-old hydrocephalic rabbit.
- Fig. 4:** (a&b) Anterio-dorsal (a) and lateral (b) views of collapsed cerebral hemispheres. 2-weeks-old hydrocephalic rabbit.
- Fig. 5:** The collapsed cerebral hemispheres were incised to show the thinness and atrophy of the cerebral tissue.
- Fig. 6:** Dilated meningeal arteriole (A). Meningeal tissue (arrow) is widely separated from the brain tissue due to edema. Note the extravasated erythrocytes (arrowhead). Hydrocephalic newborn rabbit. HE. x125.
- Fig. 7:** Yellowish-brown spots (arrow) at the meningeal surface. Microglia cells are gathered in the subcortical cerebral tissue. Hydrocephalic newborn rabbit. HE. x 280.

- Fig. 8:** Brain of hydrocephalic rabbit showing hyperplasia of ependymal Cells (arrow) lining the third ventricle. The hyperplastic ependymal cells form papillary projections into the ventricular lumen. HE. x 280.
- Fig. 9:** Subependymal focal gliosis (g) in the brain of a hydrocephalic rabbit. The ependymal lining is sloughed. HE. x 125.
- Fig. 10:** Brain of hydrocephalic rabbit showing perivascular (arrow) and pericellular edema. Shrunken neuronal cells (arrow) are also observed. HE. x 280.
- Fig. 11:** Chromatolysis of some neuronal cells (arrow). HE. x 280.
- Fig. 12:** Spongy status (reticular formation), due to demyelination, in the brain stem of a hydrocephalic rabbit. HE. x 125.
- Fig. 13:** Distorted purkinje cell layer (arrow) in the cerebellar cortex of a hydrocephalic rabbit. HE. x 280.
- Fig. 14:** Patent aqueduct of Sylvius (\*) in the brain a hydrocephalic rabbit. HE. x 125.
- Fig. 15:** Remarkable periductal gliosis (g) (gliosis surrounding aqueduct of Sylvius). The ependymal lining cells (arrow) are hyperplastic and partially sloughed. HE. x 125.







