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PATHOLOGICAL FINDINGS IN CALVES WITH HYDRANENCEPHALY[1]

Rıfkı Hazıroğlu[2]

Hidranensefalili buzağılarda patolojik bulgular[3]

Özet: *Bu çalışma hidranensefalili 22 buzağı üzerinde gerçekleştirilmiştir. Buzağıların 13'ü Alanya, 9'u İçel İli ve çevresinden, 1985 yılında seyreden epizooti sırasında sağlanmıştır. Hidranensefalili buzağılara ve bunların bazılarının annelerine ait 18 kan serumu örneğinin Pirbright Araştırma Enstitüsü'nde yapılan serolojik muayenesinde, hepsinin değişen derecelerde Akabane virusuna karşı nötralizan antikorlar içerdiği saptanmıştır. Bu serumların 8'inde ise Mavidil'e karşı ELISA pozitif sonuç alınmıştır. Ayrıca Etlik Hayvan Hastalıkları Araştırma Enstitüsü'nce çalışmada kullanılan buzağıların ikisinin kanından Mavidil virusu izole edilmiştir. İzolasyonu yapılan viruslar Pirbright Araştırma Enstitüsü'nde serotip 4 olarak identifiye edilmiştir. Buzağılarda körlük dışında belirgin bir klinik bulguya rastlanmamıştır. Makroskobik olarak, beyinde hemisferlerin değişen derecelerde serebrospinal sıvı ile dolu olduğu gözlenmiştir. Beyin stem'i ise normal görünümdedir. Corpus striatum, thalamus, hippocampus, tectum mesencephaly ve cerebellum'da basınca bağlı değişiklikler dikkati çekmiştir. Epifiz ayrılması ve hipoplazisine birer buzağıda rastlanmıştır. Ventriküler sistemde 3. beyin kamarasında kireç birikintilerinin oluşturduğu tıkanma sadece bir olguda gözlenmiştir. Çok belirgin cavum septi pellucidi, septum pellucidum'da defekt ve kısmi corpus callosum yokluğu diğer makroskobik bulgulardandır. Mikroskobik olarak, kısmen kalın olan rezidüel hemisfer dokusu normal histolojik tabakalanmayı göstermesine rağmen ince olan doku sklerotik görünümdedir. Bazı alanlarda ise sadece leptomeninksler yer almaktadır. Rezidüel hemisfer dokuları genel olarak ince bir substantia alba katından oluşmuştur ve bu katta görülen gliozis ne-*

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deniyle ana kaviteye doğru çıkıntılar yapmaktadır. İnce olan rezidüel hemisfer dokusunda görülen sklerotik görünüm, benzer şekilde hemen hemen her olguda, medulla oblongata'da promontorium gliosum calami scriptorii'de de gözlenmiştir. Ayrıca subependimal rozetler ile subepenmal gliozis, fokal gliozis, indiferansiye nöyronal nodüller, subkortikal kavitasyonlar ve hafif perivasküler infiltrasyonlar diğer bulgulardandır. Myelinasyon normaldir. Tüm olgularda görülen bu yangısal olmayan değişiklikler yanısıra bir buzağıda nonpurulent ensefalitis saptanmıştır.

Summary: *This study was based on hydranencephalic 22 calves. These calves were obtained from the provinces of Antalya and İçel during an epizootic period in 1985. The serum neutralizing antibodies against Akabane virus were detected in eighteen blood sera taken from hydranencephalic calves and their mothers by Pirbright Animal Virus Research Institute (AVRI) in England. Pozitive results for bluetongue virus were also determined in eight of eighteen sera using ELISA. In addition, the bluetongue virus was isolated from the blood of two hydranencephalic calves by Etlik Animal Disease Research Institute (ADRI) in Turkey. These isolates were identified as bluetongue virus serotype 4 by Pirbright AVRI. None the calves showed any remarkable clinical symptoms except blindness. Macroscopically, hemispheres were filled with various amounts of cerebrospinal fluid (CSF). The brain stems were normal in appearance. Changes due to compression were noticed in the thalamus. corpus striatum, hippocampus, tectum mesencephaly and cerebellum. The displacement and hypoplasia of the pineal body were encountered in two different calves. Obstruction of the third ventricle due to precipitation of calcium salts was observed in one calf. The other macroscopical findings were cystic septum pellucidum, defect of the septum pellucidum and partial absence of the corpus callosum. Microscopically, narrow residual hemispheric tissues were sclerotic in appearance, although the relatively large tissues had normal histologic structures and some areas of residual tissues were composed of only leptomeninges. Generally, residual hemispheric tissues had narrow substantia alba protruding to the membranous sacs due to gliosis. Sclerotic appearances were also observed in the promontorium gliosum calami scriptorii of the medulla oblongata in almost all of the cases. The other microscopical findings were subependymal rosettes, gliosis, subcortical cavitations and mild perivascular cuffings. Myelination was normal. These changes were found in all cases except one, that case had nonpurulent encephalitis.*

Introduction

Intracranial malformations and especially hydranencephaly have been reported in relation to prenatal infections with viruses of several families in calves. e.g. Reoviridae-bluetongue virus (15, 17, 29), Chuzan virus (7); Bunyaviridae-Akabane virus (4, 11, 12), Aino virus (4, 22); Togaviridae-bovine viral diarrhea virus (2).

In the spring of 1980, the first severe outbreak of arthrogryposis and hydranencephaly (AG / HE) in calves was reported in the western part of Turkey (33). Similar congenital deformities have been recorded in field outbreaks among the calves in Japan (13, 14, 24), Australia (5, 8, 31) and Israel (10, 16, 24), and it is generally accepted that these can be caused by the Akabane virus (4, 11–14, 20, 23). As well as this, there are indications that the bluetongue virus (BTV) may cause congenital defects in the central nervous system (CNS) both in the field and laboratory (15, 17, 26, 27, 29). Secondly, another outbreak characterized only hydranencephaly was observed in calves in the southern part of Turkey in 1985 / 86.

This paper presents the results of a study of the pathology of 22 affected calves from the southern part of Turkey in 1985.

Materials and Methods

A total of 22 hydranencephalic calves were supplied from the provinces of Antalya and İçel between May 1985–July 1985: 13 from the region around Antalya and 9 from the region around İçel. Table 1 shows calves' age, brain weight, breed, sex and origin.

Calves no 21 and 22 were conveyed to the University of Ankara, Faculty of Veterinary Medicine, Department of Clinical Sciences for clinical examination, electroencephalography (EEG) and electrocardiography (ECG) on July 12, 1985.

Blood sera samples relating to the first 11 calves and some of their mothers were sent to Pirbright AVRI, for examination of neutralizing antibodies against the Akabane and bluetongue viruses.

Following a clinical examination of the live animals apart from numbers 1, 2, 3 and 4, they were necropsied. The brain and spinal cord were removed and a gross examination was made. The complete

Table 1. Age, brain weight, breed, sex and origin of the calves used in this study.
Tablo 1. Çalışmada kullanılan buzağıların yaş, beyin ağırlığı, ırk, seks ve orijinleri.

Calf no	Age (Month)	Brain weight(g)[X]	Breed	Sex	Origin
1	2	75	Unknown	F	Antalya
2	1.5	44	"	M	"
3	2	58	"	M	"
4	2	57	"	F	"
5	3	111	Hc	M	"
6	1.5	65	"	M	"
7	1.5	50	"	F	"
8	3	69	"	M	"
9	2	85	"	F	"
10	3	94	Lb	F	"
11	2	68	Hc	M	"
12	3	100	"	F	İçel
13	2.5	68	"	M	"
14	4	91	"	M	"
15	2	75	Lb	F	"
16	5.5	107	Hc	F	"
17	4	127	Lb	F	"
18	5	112	Hc	F	"
19	1.5	101	"	F	"
20	4.5	118	"	F	"
21	10.5	95	"	M	Antalya
22	14	134	"	M	"

X After formalin fixation (Formalin fikzasyonundan sonra)
F Female (Dişi)
M Male (Erkek)
Hc Holstein crossbreed (Holştayn melezi)
Lb Local breed (Lokal ırk)

range of other organs and tissues were taken from the calves. Following fixation with 10 % buffered formalin the brains were weighed and sliced transversally (Fig. 1) and gross lesions recorded. Tissue samples were taken from the brain and cord, and other viscera. These were processed for histological examination by conventional methods. Sections were stained with haemotoxylin and eosin (HE) and selected sections from the CNS were also stained with Klüver and Barrera's luxol fast blue (LFB) for myelin-Gomori's method for reticulum fibers and Holzer's method for neuroglial fibers.

Results

Clinical findings: The major defect was a lack of intelligence, and blindness. In a small series tested, the eye preservation reflexes were absent, but pupillary light reflexes were present. They were dummies,

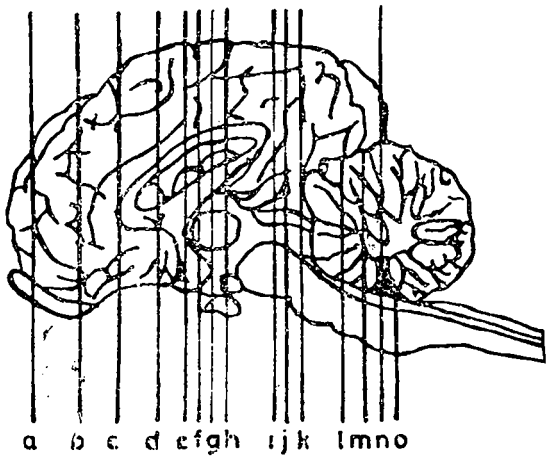

Fig. 1. The coronal sections taken from affected brains for microscopic examination (Şekil 1. Mikroskobik inceleme için lezyonlu beyinlerden alınan koronal kesitleri gösteren şema).

uncoordinated in gait, unable to stand properly and moved erratically when stimulated. The calves showed cud chewing behaviour as if fodder existed inside their mouths and exhibited licking action, Pulsation, temperature and respiration were normal and they had hearing abilities. Other clinic observations were salivation, vomitus, nervous symptoms such as convulsion and tremor, lacrimation, strabismus, domed cranium and torticollis in different calves. In the calves transported from Antalya to Ankara, there were insignificant activities of neurons in EEG and ECG was normal. Pirbright AVRI's results are shown table 2.

Gross pathology of the central nervous system: The cerebral hemispheres or major parts of them were represented by a fluctuant fluid-filled sac bounded by a thin delicate membrane which was attached to the meninges and which frequently collapsed as the calvarium was removed. The fluid was watery and clear or blood-stained. Occasionally the hemispheric lesions were asymmetrical and occasionally symmetrical. Cystic cavities were found in the residual hemispheric tissues and midbrain. They were located in areas bilateral or unilateral to the mesencephalic canal. Although the brain stem appeared unchanged from the exterior, cross sections showed solitary and multiple cystic cavities of various sizes in the nerve tissue. Particularly large cavities, approximately 0,5 cm in diameter were observed in the residual

Table 2. Results of ELISA test and SVNT carried out on blood sera of calves for BT and Akabane viruses, respectively.

Tablo 2. Mavidil ve Akabane virusları için buzağıların kan serumlarında yapılan ELISA ve SVNT (serum virus nötralizasyon testi) testleri sonuçları.

Calf no	BT (Elisa)	Akabane (SVNT)
1	—	1:192
2	—	1:192
3	—	>1:384
Mother of calf 3	—	1:256
4	—	1:128
5	—	1:64
6	+	1:96
Mother of calf	+	>1:384
7	+	1:96
Mother of calf 7	+	1:192
8	+	>1:384
Mother of calf 8	+	1:96
9	?	1:64
Mother of calf 9	+	1:96
10	?	1:48
Mother of calf 10	+	1:96
11	—	1:64
Mother of calf 11	—	1:192

hemispheric tissues (Fig. 2). The inner surface of the cavity was usually moist, with a slight accumulation of CSF.

After formalin fixation brain weight (Table 1) ranged from 44 to 134 g (normal 180–250 g). The spinal cord appeared normal in size and did not have any macroscopic lesions.

Most of the cases had small nodular masses of 1–2 mm in diameter on the leptomeninges, corpus callosum and nucleus caudatus. Partial absence and defect of the corpus callosum were observed in some brains. Total absence and defects were also observed in the septum pellucidum. Moreover, cystic septum pellucidum called double septum or 5 th ventricle or cavum septi pellucidi anatomically was found in one case (Fig. 3). In some cases, the septum pellucidum was intact, but extremely thin. There were deformities in the shape of the nucleus caudatus, thalamus, mesencephalon and cerebellum. These deformities could be due to the compression of the hemispheres which were full of fluid. Another marked finding was band-shaped residual brain tissues between corpus callosum-residual hemispheres, nucleus caudatus-residual hemispheres, and residual hemispheres-residual hemispheres (Fig. 4). The hippocampus was greatly reduced unilaterally or bilaterally and in some of the cases a granular surface was observed. The ventral portion of the cerebrum became as thin as a shell because

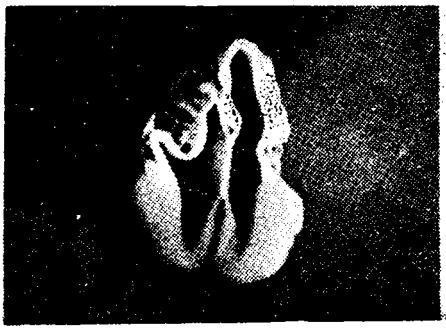

Fig. 2. The cystic cavitations of the residual hemispheric tissue sectioned from the lobus frontalis. Case no 19.
(Şekil 2. Lobus frontalis'ten arta kalan hemisferik dokudan yapılan kesitteki kistik kavitasyonlar. Olgu no 19).

Fig. 3. Cystic septum pellucidum. Case no 5.
(Şekil ?. Kistik septum pellucidum. Olgu no 5)

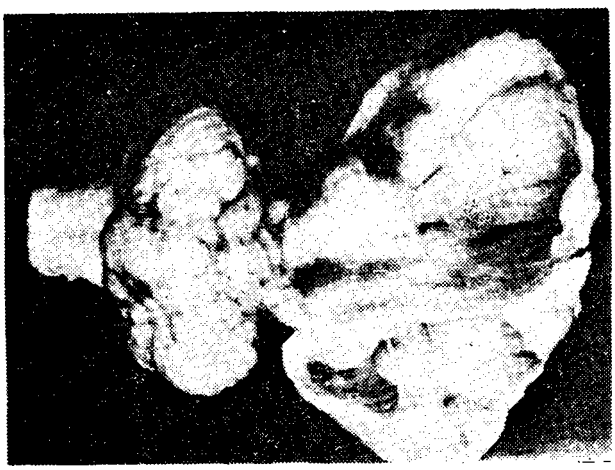

Fig. 4. Hydranencephalic brain, slight cerebellar hypoplasia, and band-shaped residual nerve tissue. Case no 7.
(Şekil 4. Hidranensefalik beyin ,hafif serebellar hipoplazi ve band şeklindeki kalıntı sinir dokusu. Olgu no 7)

of the nearabsence of the frontal temporal and parietal lobes. As a result, the corpus striatum, thalamus and hippocampus were exposed. The other macroscopical findings were obstruction of the 3 rd ventricle (Fig. 5), displacement and hypoplasia of the pineal body (Figs. 6, 7), dilatation of the mesencephalic canal (Fig. 8) and a crateriform appearance of the tectum mesencephaly.

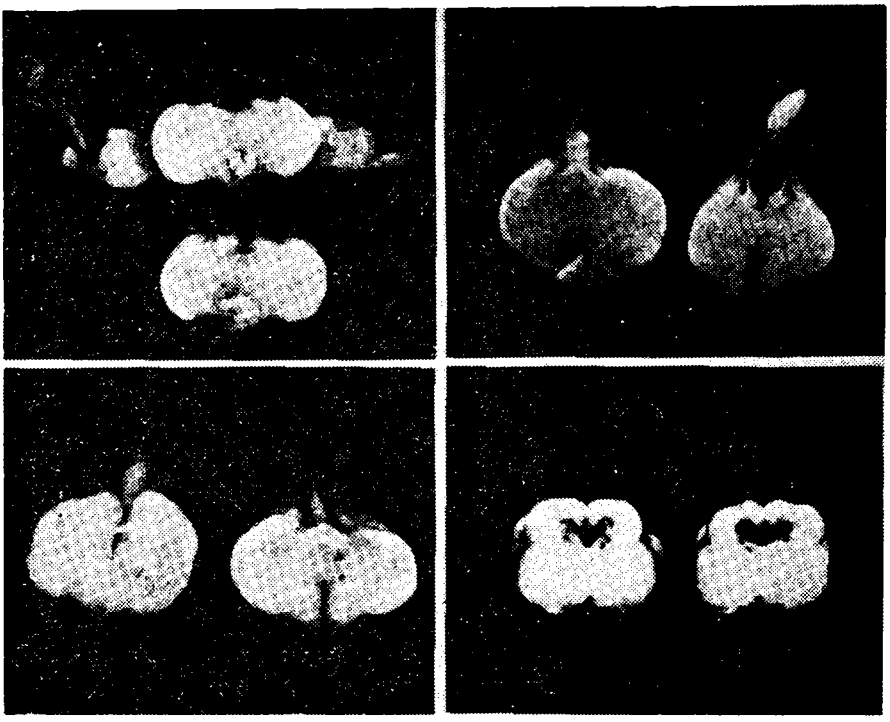

Fig. 5. Obstruction of the third ventricle due to calcium salts. Case no 2.
(Şekil 5. Kalsiyum tuzlarının neden olduğu 3. ventriküldeki tıkanma. Olgu no 2)
Fig. 6. Displacement of the pineal body. Case no 20, 16.
(Şekil 6. Epifizis serebrinin normal konumundan ayrılması, Olgu no 20, 16)
Fig. 7. Hypoplasia of the pineal body. Case no 20, 18.
(Şekil 7. Epifizis serebrinin hipoplazisi. Olgu no 20, 18)
Fig. 8. Dilatation and cystic cavities around the mesencephalic canal. Case no 2.
(Şekil 8. Mezensefalik kanal çevresinde kistik kavitasyonlar ve genişleme. Olgu no 2)

A Slight cerebellar hypoplasia (Fig. 4). herniation and irregularity of the folium were encountered in some calves.

Gross pathology of other tissues and organs: There were no consistent associated lesions outside the brain. The wounds of the back and legs, subcutaneous haemorrhages of the head and legs, subcutaneous jelatinous accumulations and hepatisation of the cranial lobes in the lungs were observed in calves nos 13, 14, 15 and 16, respectively. Apart from pneumotic lesions in the lungs, these must be traumatic due to blindness. There were no pathological changes in the eyes and optic nerves.

Histology of the central nervous system: Hydranencephaly was characterized histologically by a cerebral cortex so thin that at low magnification it fitted into one microscopic field. Its internal surface with ependymal cells was frequently incomplete or absent. Abundant mesodermal fibers associated with numerous capillaries were observed in the residual hemispheric tissues (Fig. 9), corpus callosum, septum pellucidum, hippocampus, thalamus, pineal body, hypophysis, mesencephalon and promontorium gliosum calami scriptorii of the medulla oblongata. These gave a sclerotic appearance to the tissue (Fig. 10). The thin residual hemispheric tissues were sclerotic in appearance (Fig. 11), although the relatively large tissues had a normal histologic structure and some areas of residual tissues were composed of only leptomeninges.

There were also glial infiltrations, both nodular and diffuse, in the vicinity of the ependymal lining. Quite often these glial nodules were seen to protrude into the ventricles or mesencephalic canal.

Cystic cavitations, subependymal rosettes, mineralisations, microhaemorrhages and spongiotic areas were observed in various parts of the CNS, and subcortical cavitations. substantia grisea- substantia alba-substantia grisea or mixed structure (Fig. 12) were seen in the residual cerebral cortex in some cases. Ependymal dysplasia located in the vicinity of the central canal was also found.

The cystic cavities were a space formed in the nerve tissue without any special type of wall, in which both nerve cells and nerve fibers dissappeared completely. Neuroglial cell infiltrated into the cavity and often mixed with fragments of nerve fibers or the cavity was totally empty under the microscope (Fig. 13). The nerve tissue around the cavity was destroyed and there was disruption and rarefaction of nerve fibers or was packed with CSF under pressure.

The cavitation was of perivascular origin, and was probably influenced by the excess pressure of the CSF. The Wirchow-Robin spaces became extremely dilated. The CSF invaded the nerve tissue adjacent to the perivascular space, which then disrupted and dissappeared. A cavity involving blood vessels eventuall formed in or near this space. These types of cystic cavities were especially found in the mesencephalon and rhombencephalon.

It is known that ependymal roset formation in congenital encephalopathies is often seen in the subependymal areas along the ventricles.

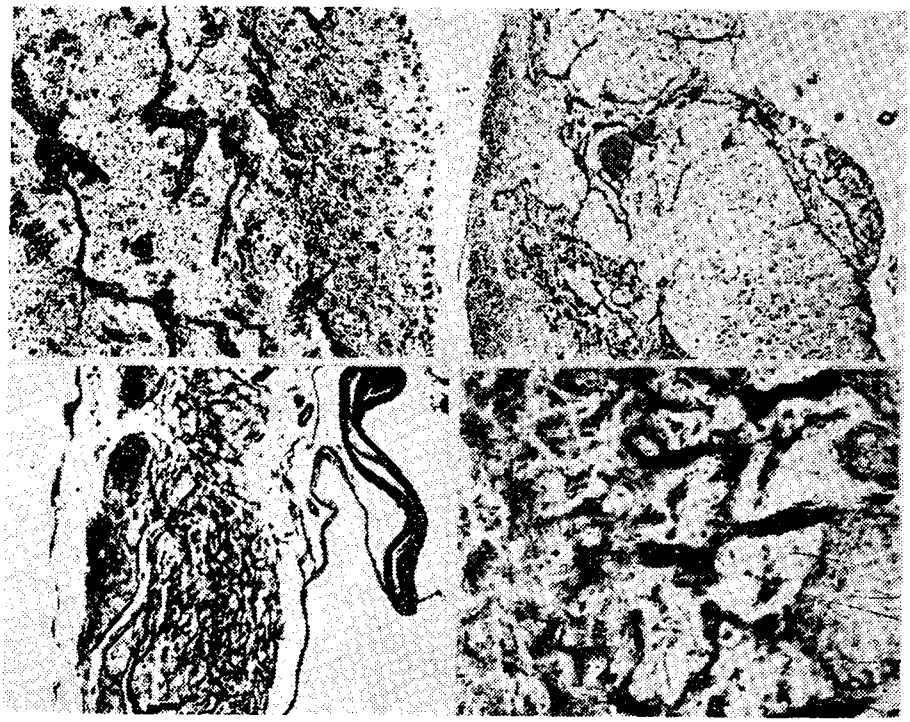

Fig. 9. Abundant argentaffin fibers in close association with numerous blood vessels in the residual hemispheric tissue. Case no 15, Gomori's reticulum stain.
(Şekil 9. Arta kalan hemisferik dokuda yer alan çok sayıdaki kan damarları ile yakın ilişkili argentaffin fibriller. Olgu no 15, Gomori'nin retikulum boyası)
Fig. 10. Sclerotic appearance in the residual hemispheric tissue. Case no 11, HE
(Şekil 10. Arta kalan hemisferik dokudaki sklerotik görünüm. Olgu no 11, HE)
Fig. 11. Complete sclerotic appearance in the narrow residual hemishpheric tissue. Case no 7, Gomori's reticulum stain.
(Şekil 11. Arta kalan dar hemisferik dokudaki tam sklerotik görünüm. Olgu no 7, Gomori'nin retikulum boyası)
Fig. 12. Mixed substantia alba and grisea in the cerebral cortex. Case no 2, Klüver Barrera's myelin stain.
(Şekil 12. Serebral kortekste birbirine girmiş substantia alba ve grisea. Olgu no 2, Klüver Barrera'nın myelin boyası)

Subependymal rosettes were also observed in all calves (Figs. 14, 15) except calf no 22. As well as this, some ependymal rosettes were found in the deep part of the nerve tissue. These may depend on pressure of the CSF.

A few small foci of mineralisation, which probably developed during the growth of the brain, occurred in the residual hemispheric tissues,

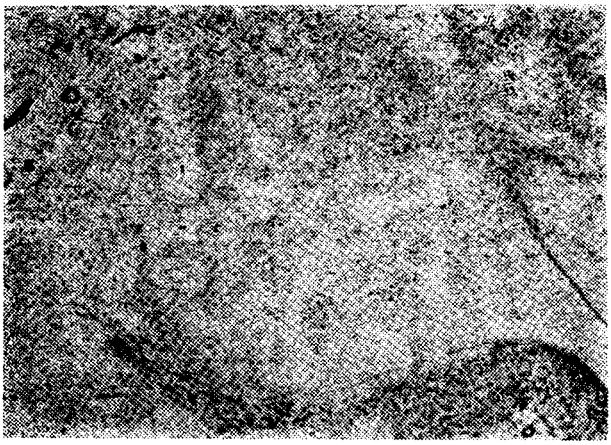

Fig. 13. Subcortical cavitations and a few mineralisation foci in the cerebral cortex. Case no 19, HE.
(Şekil 13. Serebral kortekste subkortikal kavitasyonlar ve az sayıdaki mineralizasyon odakları. Olgu no 19, HE)

thalamus (Figs. 13, 16). pineal body and hypophysis. The obstruction of the 3 rd ventricle due to calcium salts was observed in one calf. Furthermore, this type of calcium precipitate was free in the bases of the hemispheric sacs of some of the affected brains.

Deformities in the shape of the cerebellum, probably due to CSF compression were encountered and they showed no remarkable pathological changes except that case no 7 and case no 2 had hypoplastic changes including depletition of the external granular layer, Purkinje cell ectopia, and reduction in the width of the granular or molecular layer. In these affected cases, the cortical architecture was disturbed, foliation was rudimentary and islands embedded within the substance were surrounded by Purkinje and granular cells (microgyria) (Fig. 17).

Two calves (Calves no 11 and 12), which were not able to walk during their life, exhibited microhaemorrhages in the lateral and ventral horn of the medulla spinalis.

Myelination was normal in the sections stained by the LFB method. A marked systematic increase in glial fibers was frequently seen in the periphery of the dilated perivascular spaces, the wall of the ventricles and cavities in sections stained with Holzer's method.

Inflammatory changes were not found in the CNS of the calves except that calf 22 had marked nonpurulent encephalitis.

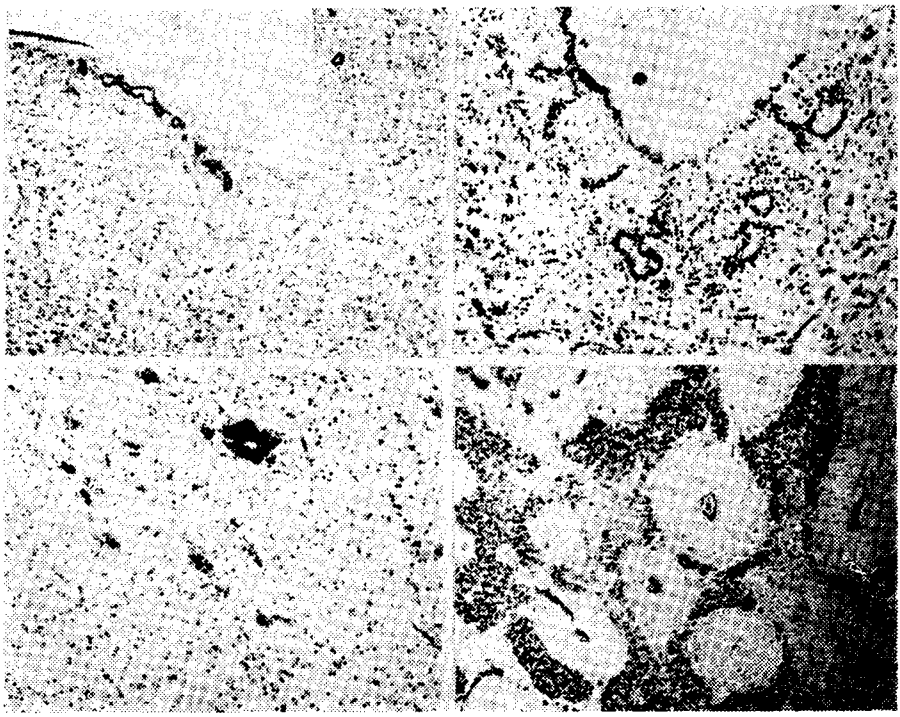

Fig. 14. Partial absence of the ependymal layer in the 3 rd ventricle and subependymal rosettes. Case no 6, HE.

(Şekil 14, Üçüncü ventrikülü döşeyen ependim hücrelerinin kısmi yokluğu ve subependimal rozetler. Olgu no 6, HE)

Fig. 15. Close magnification of the subependymal rosettes. Case no 15, HE

(Şekil 15. Subependimal rozetlerin daha büyük görünümü. Olgu no 15, HE)

Fig. 16. Mineralisation in the thalamus. Case no 14, HE

(Şekil 16. Talamusta mineralizasyon. Olgu no 14, HE)

Fig. 17. Coronal sections of the cerebellum. The Purkinje and granular cells as islands are displaced into the molecular layer. Case no 7, HE

(Şekil 17. Serebellumun koronal kesiti. Moleküler tabakaya doğru yer değiştirmiş Purkinje ve granular hücrenin oluşturduğu adacıklar. Olgu no 7, HE)

There were no lesions in the eyes and optic nerves histologically in any of the cases examined for this.

Discussion and Conclusion

In Turkey, bluetongue disease (BTD) in sheep was first clinically diagnosed in the south of the country, in 1944 (1). After a 30-year break, there were 19 separate outbreaks in southwestern Turkey in 1977 and

spread to other areas in the same region in 1978 and 1979 (1, 30, 35). In that period a virus isolated from a sheep was identified as BTV serotype 4 (35).

In March 1980, the first outbreak of AG / HE in calves in the south-western part of Turkey was reported (33). In May 1980 serological investigations carried out on blood collected in western Turkey showed antibodies to Akabane virus in adult cattle and calves and in a colostrum-deprived calf. However, the Akabane virus was not isolated. In October 1980 BTV serotype 4 was isolated from a newborn calf with AG / HE (35).

Almost five years later, in May 1985, we observed another outbreak in calves around Antalya and İçel in the southern part of Turkey (Fig. 18) which manifested itself only by hydranencephaly. Also, some of these calves and some of their mothers had antibodies to the Akabane virus and some were positive against BTV. In view of the fact that these calves had taken colostrum, it is difficult to evaluate whether it is active

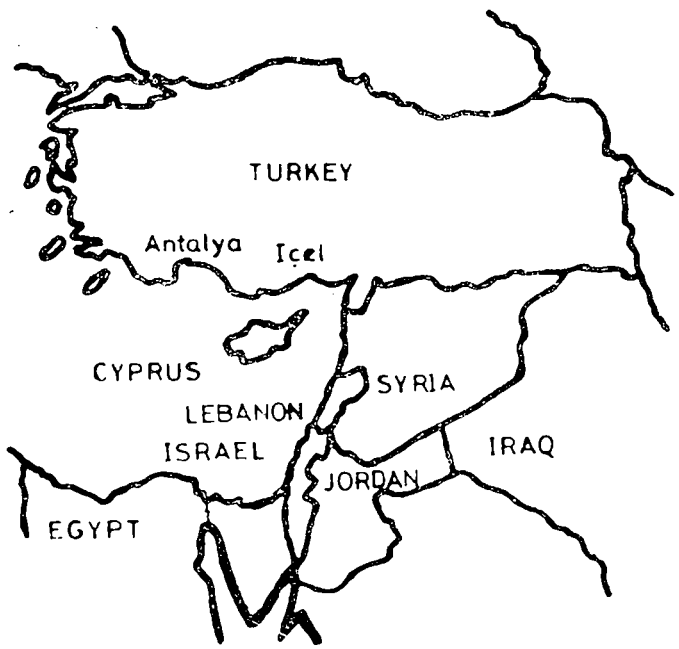

Fig. 18. Provinces involved in the outbreak in calves between 1985 and 1986, and location map of Turkey.
(Şekil 18. Türkiye'de buzağılarda 1985—1986 yıllarında hastalığın görüldüğü bölgeler)

immunity in the calf or it is obtained from the mother. In addition, BTV was isolated from calves nos 5 and 17 by Etlik ADRI and identified as serotype 4 by Pirbright AVRI.

Bluetongue and Akabane viruses are transmitted by biting midges of the genus Culicoides (6, 9, 18, 30) or mosquitoes (19, 28). Central nervous system anomalies have been observed in calves born to dams exposed by BTV, Akabane virus and other viruses -e.g., bovine viral diarrhea, Aino, Chuzan- in the first trimester of pregnancy (11, 15, 23, 26). In the last outbreak, similarly, pregnant cows could have been infected by the virus or viruses at the end of summer 1984 by midges. However, there is no data on Culicoides movements or on meteorological conditions, but it is possible that during suitable weather conditions, biting midges may migrate from other mediterranean countries and this became active in the southern part of Turkey. Also, there is serological evidence of Akabane activity in Cyprus, Israel, Northern Syria and Jordan (Fig. 18) (P.S. Mellor, personel communication).

Clinical and macroscopical findings in hydranencephalic calves were almost identical with the literature (8, 11, 15, 21, 24, 29, 34) except the obstruction of the 3 rd ventricle, displacement and hypoplasia of the pineal body and cystic septum pellucidum. Cystic septum pellucidum has been encountered in newborn lambs which their dams infected with pestiviruses (3), but have not been recorded in calves. For the first time, these macroscopical findings are being reported in calves with hydranencephaly.

Also, histological findings reported were similar to those of our cases (8, 11, 15, 21, 24, 29, 34). The sclerotic structure was recognized in various parts of CNS of the calves. It is noted that sclerotic appearance of the superior and inferior colliculi is a constant and interesting feature of hereditary encephalomyopathy in Hereford calves (32), whereas it was not considered to be hereditary in our cases. Since most of our cases were third or fourth calves and the first or second calves born to the same mother suffered no congenital deformities or CNS anomalies we ruled out all congenital defects. As well as this, the breeds of our cases were different. The CSF may have caused reactivity of the glial tissue resulting in dense fibrillary gliosis and this may give a sclerotic view to the tissue. In this condition, it can be seen in every cases exposed by the pressure of the CSF, but it has not been previously recorded in hydranencephalic calves.

Marked nerve cell loss with fibrillary gliosis in the ventral horn of the spinal cord and in the nucleus fasciculi lateralis, nucleus nervi hypoglossi and nucleus dorsalis nervi vagi of the medulla oblongata have been noted in calves with AG / HE (21). Our cases were only hydranencephalic and there were no marked lesions except haemorrhages in the spinal cords and in those of the nuclei of the medulla oblongata.

In this complicated situation, we believe that the etiology of these outbreaks is still obscure. BTV and Akabane virus together or separately may be the causative agents of these outbreaks. Epidemiologic, serologic and virologic studies are needed to elucidate this condition in Turkey. A project is in progress for this purpose.

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