LESIONS OF THE HYPOTHALAMUS, ADENOHYPOPHYSIS, AND THE OVARIES IN TRYPANGOSMA VIVAX – INFECTED YANKASA, EWES

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SUMMARY

Twelve mature nonpregnant Yankasa ewes (6 control and 6 experimental) were used to study the effects of experimental T. vivax infection on the ovaries, adenohypophysis (anterior lobe of the pituitary gland) and the tuberal region of the hypothalamus. The ewes were sacrificed at the end of 50 days post infection. The weight of the ovaries were taken while the ovaries, tuberal part of the hypothalamus and the adenohypophysis were processed for histopathology. The ovaries of all the infected ewes showed marked atrophy, coupled with an extensive hyalinization of the ovarian stroma. The lesions in the hypothalamus of the infected ewes were marked by extravasations of blood while those of the pituitary glands were characterized by mononuclear (mostly lymphocytes and macrophages) cellular infiltration into the capsules and the parenchyma along with necrosis of the parenchymal cells.

It was suggested that these lesions might underline the basis of some of the earlier reported clinical and endocrinological indications of infections with T. vivax in animal models.

KEY WORDS: Trypanosomiasis, lesions of ovary, adenohypophysis, and hypothalamus, Yankasa ewes

INTRODUCTION

Sterility, menstrual disorder, abortions and still-births had been reported by Apted (1970) in human patients suffering from African trypanosomiasis (sleeping sickness). Progressive weight loss of about 17.9% of the original body weight was reported in T. vivax infected ewes (Adenowo et al. 2004) while abortion and general infertility were equally reported by O’hara et al. (1985) in ruminants. Though an increasing number of reports are available on histopathology of the hypophysis and gonads of trypanosoma – infected animals (Ikede, 1979; Anosa and Isouir 1980), the pathogenesis of these lesions is not too clear due to the availability of very few detailed clinical, pathological and endocrinological studies in this regard. One of such studies was carried out to appraise the pathogenic mechanisms leading to the neurological phase of human African trypanosomiasis in animal models (Darsaud et al., 2003). In their study, trypanosomes and inflammatory cells were detected histologically in the choroid plexus of the infected rats, the results of which, favored the central nervous system functional disturbances as the neurological symptoms observed in human disease, reproduced in the rat model.
Recent evidence suggested that experimental trypanosomiasis caused polyglandular endocrine failure by local inflammation of the pituitary and gonadal glands (Reincke et al., 1998). Although, Waindi et al. (1986) reported trypanosome-induced depression of testosterone in bulks and deteriorations of the semen in ram (Sekoni, 1992), reduced ovulatory activity and disrupted oestrous cycles had also been reported in ewes infected with *T. congolense* (Luckins, et al., 1986); ewes infected with *T. vivax* (Elhassan et al., 1994) and Zebu heifers following *T. vivax* infection (Obasi et al., 1990).

Adenowo (1989) had earlier documented the clinical and the endocrinological observations in Yankasa ewes experimentally infected with *T. vivax*. This paper therefore reports the lesions in the hypothalamus, anterior lobe of the pituitary gland and the ovaries of these experimental animals.

**MATERIALS AND METHODS**

Twelve normally cycling mature nonpregnant Yankasa ewes (6 experimental and 6 control) were used for this study. Only the experimental ewes were intravenously inoculated with 10 ml of sheep blood containing about $3.5 \times 10^7$ *T. vivax* (strain Kabam/84 – NITR – 14). All animals were accommodated in a fly-proof house, where they were acclimatized for 6 months before the commencement of the study. The animals were fed 2% body weight of concentrates, local gamba hay, water and mineral salt – *libitum* throughout the experiment.

**Histopathology**

Animals were sacrificed at the end of 2 normal oestrous circles (about 50 days) following *T. vivax* infection in the experimental ewes. The ovaries were weighed on an electronic chemical balance (Mettler-P. 163). The left and the right ovaries were also examined grossly. The ovary, adenohypophysis and the tuberal part of the hypothalamus were fixed in 10% formol-saline and Bouin’s fluid and processed for routine histopathology (Junqueira et al., 1975); embedded tissues were sectioned at 7 microns and stained with Haematoxylin and Eosin (H & E). The Olympus light microscope was used to examine all the slide-preparations for histopathological lesions.

The mean data of infected and control animals were compared statistically by the students – *t*– test (Winer, 1971).

**RESULTS**

Histopathological observations in the tuberal region of the hypothalamus, the anterior lobe of the pituitary gland and the ovaries of *T. vivax* infected ewes were similar although the severity of the lesions varied from one experimental animal to the other.

**The Ovaries in Experimental Group**

The mean ovarian weights (Table I) of the infected ewes were reduced about half of the control weight ($P < 0.01$). This was more apparent when the ovarian weights were expressed as percentage of the final body weight (Table I). Histopathologically, the control ewes had normal ovaries containing variable numbers of primordial to graafian follicles (Fig. 1). In contrast, the ovaries of the infected ewes showed various degrees of lesions which ranged from mild fibrosis of the ovarian stroma characterized by the presence of extensive fibrous connective tissue and atretic follicles with no trace of tertiary and graafian follicles (Fig. 2); to extensive fibrosis characterized by
hyalinization of the ovarian stroma with no evidence of corpus – luteum (CL.) and follicular development (Fig. 3).

TABLE I: Ovarian weights in T. vivax infected and control ewes

<table>
<thead>
<tr>
<th>Group</th>
<th>Ovarian weights(a)</th>
<th>% body weight</th>
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<tr>
<td>Control (n = 3)</td>
<td>1.31 ± 0.28</td>
<td>0.009 ± 0.001</td>
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<tr>
<td>Infected (n = 6)</td>
<td>0.65 ± 0.00(b)</td>
<td>0.005 ± 0.001</td>
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\(a\) = mean  
\(b\) = significantly different from corresponding controls (p< 0.01)

Changes in the Anterior Lobe of the Pituitary Gland
The histopathological lesions in the anterior lobe of the pituitary gland were characterized by mononuclear (mostly lymphocytes and macrophages) cellular infiltration into the capsules and the parenchyma (Figs. 4 and 5). Most of the acidophilic and basophilic cells were necrotic with dark pyknotic nuclei and faintly stained cytoplasm. Few tissue structures and cellular outlines could still be seen in some areas (Fig. 5). There were no pituitary lesions in the control ewes.

Fig. 1: Ovary of control ewe showing Graafian follicle embedded in paranchymal cells and dense irregular connective tissue. H & E x400

Fig. 2: Ovary of infected ewe showing mild fibrosis of the ovarian stroma with extensive fibrous connective tissue and atretic follicles. H & E x400

Fig. 3: Ovary of an infected ewe showing extensive fibrosis of the ovarian stroma with no evidence of follicular formation. H & E x400

Fig. 4: Anterior pituitary lobe of an infected ewe showing mononuclear cell infiltration into the capsule and paranchyma. H & E x200

Fig. 5: Anterior pituitary lobe of an infected ewe showing necrosis and fibrosis of the paranchymal cell groups (right wing of micrograph). H & E x 400

Changes in the Tuberal region of the Hypothalamus
Generally, the lesions in the tuberal region of the hypothalamus of the infected ewes consisted of generalized extravasations of blood into the stroma. (Fig. 6) while the tuberal region of the hypothalamus of each control ewe showed no histopathological

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lesions but normal nerve cells and neuropil stroma.

Fig. 6: Tuberal region of the hypothalamus of an infected ewe showing generalized haemorrhage (arrowed). H & E. x400.

DISCUSSION

The exact mechanisms by which *T. vivax* adversely affect reproduction are poorly understood. Several causes have been suggested, which include pituitary hormonal defects in man (Apted, 1970), in goats (Griffin and Allonby, 1979), and in sheep (Ikede and Losos, 1972). Depressed plasma progesterone levels had been associated with degenerative lesions of the hypothalamus, pituitary glands and the ovaries in *T. vivax* infected ewes (Adenowo, 1989).

The histopathology of the ovaries, anterior lobe of the pituitary gland and the tuberal region of the hypothalamus of *T. vivax* infected ewes observed in this study agrees with earlier observations such as reduction of overall size of the organs and extensive tissue damage, affecting the central nervous system, endocrine and reproductive organs in *T. vivax* – infected sheep and goats (Losos and Ikede, 1972; Anosa and Isoun, 1980; Darsaud et al., 2003), in *T. brucei* – infected sheep and goats (Ikede and Losos, 1972) in *T. congoense* – infected sheep and goats (Luckins et al., 1986; Mutayoba et al., 1995) and guinea-pigs (Omeke and Onuora, 1992).

Apart from fever (Griffin and Allonby, 1979), anaemia (Adenowo et al., 2004) and stress (Ikede, 1979); *T. vivax* has greater chances of causing the observed lesions through the humoral hypersensitivity, formation of immune complexes and toxins which are made much more injurious to the tissues by the sequential surface antigenic changing of these parasites during each wave of parasitaemia (Murray et al., 1975). However, an autoimmune origin of the endocrine abnormalities observed in African trypanosomiasis was ruled out (Reincke et al., 1998). This was due to the absence of pituitary, thyroid, adrenal and gonadal autoantibodies in patients with such endocrine dysfunctions. Hypopituitarism was however observed to correlate with high cytokine concentrations in their investigation. This, together with the direct parasitic infiltration of the glands were implicated in the pathogenesis of sleeping sickness (African trypanosomiasis) – associated endocrine dysfunctions.

The presence of the efferent projections of the arcuate nucleus (ininfundibular nucleus) of the tuberal region of the hypothalamus into the external layer of its median eminence had been observed (Carpenter, 1991). Since the median eminence of the hypothalamus had been found to be the anatomical interface between the brain and the anterior pituitary gland, its anterior connection with the arcuate nucleus is thus of great importance to the adenohypophyseal functions. In this regard, chemical substances (releasing factors) from the arcuate nucleus of the hypothalamus play a major role in the regulation of hormonal output from the anterior pituitary; transported via the hypophyseal portal vessels (Page, 1988).
Hence, the pituitary lesions observed in this study may underline the various estrus abnormalities earlier reported (Adenowo, 1989), namely: silent estrus, partial anestrus and total anestrus. The observed significant reduction in the relative weight of the ovaries of the infected ewes might have been due to body weight loss in these ewes (Darsand et al., 2003, Adenowo et al., 2004). However, the pathology of the hypothalamic-pituitary-ovarian axis in this investigation may explain the basal progesterone profiles earlier reported in estrus dysfunctions in T. vivax infected Yankasa ewes.

Disorders at any level of the hypothalamic pituitary – ovarian axis may therefore cause reproductive failure, ranging from the extreme of a total lack of ovulation (anovulation) to a poor quality of ova and corpus luteum produced, leading to irregular ovulation. The hypothalamic – pituitary and ovarian lesions observed in our studies may also be due to intermittent pyrexia observed throughout the period of the experiment (Adenowo et al., 2004). However, Elhassan et al. (1994) found neither gross nor histopathological lesions in the endocrine/reproductive organs of T. vivax infected West African Dwarf ewes.

In conclusion, our main finding was that experimental T. vivax infection resulted in histopathologic damage of the tuberal part of the hypothalamus, the adenohypophysis and the ovaries of mature, nonpregnant Yankasa ewes. These observations may explain the earlier reports of clinical reproductive failures and endocrine dysfunctions in African trypanosomiasis of both human and other lower animal models.

Hence, these results further showed that T. vivax infection adversely affected animal reproduction through interference with the hypothalamic-pituitary-ovarian axis in Yankasa ewes.

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