Histopathological alterations in thyroid gland of rabbits treated with lithium carbonate

İbrahim ASLAN[1], İsmet AYDIN[1], Yusuf NERGİZ[2], Mithat BAHÇECİ[1], M Aydın KETANI[3]

Depts. of [1] Endocrinology & Metabolism and [2] Histology & Embryology, Medical School of Dicle University,
[3] Health Science Research Centre of Dicle University (DÜSAM), Diyarbakır, TURKEY

Lithium carbonate is an antimanic agent which is capable of leading to morphological and functional alterations in the thyroid gland. The actions of lithium carbonate on thyroid gland have therefore been investigated in rabbits exposed to lithium medication orally for 45 days at the dose of 20 mgjkgjday. Histopathological examination of the thyroid gland by light microscope and assaying antithyroid antibody were taken into account in evaluating the mechanism of thyroid abnormality. The appearances of the thyroid glands were compatible with simple diffuse goitre in different stages. The antithyroid antibodies were found to be positive just in a few occasions and in a few number of female rabbits. Together these datas indicate that: 1) The effects of lithium carbonate on thyroid gland are more complicated than the effects previously reported causing auto immune thyroiditis or hypothyroid developments. 2) The direct cytotoxic effect of lithium appears to be influenced by gender and gene expressions. 3) The further works covering tissue cultures and local growth factors would offer much more information about the pathogenesis for morphological and functional alterations.
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Key Words: Lithium, Goitre, Antimicrosomal antibody, Antithyroglobulin antibody

Morphological alteration in the thyroid gland and thyroidal dysfunction have been reported previously in patients treated with lithium carbonate (1). It was noted that lithium evokes exacerbation of an underlying indolent autoimmune thyroiditis, possibly by causing shifts **in** T-lymphocyte subpopulations (2). This conclusion was based on a marked increase in anti thyroid antibody titre after lithium treatment. The thyroid gland specimens of lithium treated rats were previously examined under light microscope and definitive morphologic alterations were noted. Significant reduction **in** the epithelial height and an increment in coloidal content suggesting a hypothyroid condition were the main histopathological changes (3). In one of the other studies, intracytoplasmic crystalline bodies of various sizes which were surrounded by small micro vesicles or endosed in larger vesicle have been reported in thyroid cells of younger mice under chronic lithium treatment (4). This crystalline pattern was considered as a result of the deficiency of thyroid cell metabolism related to lithium (4).

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Correspondence: Ismet AYDIN
Department of Endocrinology and
Metabolism Medical School of
Dicle University, Diyarbakir,*TURKEY

However, there is no clear cut explanation about lithium induced morphological alteration in the thyroid gland. Additional studies covering lithium treatment and histopathologic evaluation of the thyroid gland following treatment in rabbits would be helpful to understand lithium effect on thyroid pathology.

MATERIALS AND METHODS

In this experiment 20 adult New Zealand albino rabbits consisting of 10 male and 10 female with an averaged weight of 2113±420 grams were studied. All of the rabbits were fed by specially daily prepared drinking water containing 20 mg/kg day dose of lithium carbonate for 45 days. Before the experiment and during the medication all of the animals were given a standard pellet chow which contained 2-4 mg/kg iodine for each day. Blood samples were drown via 21 gauge needles inserted in ear vein. On six occasions (at basal, 7,15,30,45,60th days) blood was obtained to assay anti thyroid antibody. The samples were centrifuged promptly, plasma was separated and stored at -20°C until the time of the antibody assay. Antithyroglobulin and antimicrosomal antibody were assayed by using Boyden's passive hemagglutination methods. Welcome thymune-M kit and Welcome thymune-T kit were used in this assay system.

Two months after starting medications, the rabbits were sacrificed, the thyroid gland was removed and weighed. The fragments of the thyroid gland were fixed by using 10% formaldehyde and embedded in paraffin. Obtained paraffin sections were stained with haematoxylin-eosin and Mason's trichrome. Histopathological appearances have been evaluated by light microscope.

RESULTS

The effect of lithium medication on the level of anti thyroid antibodies: Anti thyroid antiLody titration and the time of appearance in antibody positive animals are shown in Table 1. In one of the rabbits, antimicrosomal antibody was positive before medication but after seven days of the treatment it was found negative. The occurrence of antithyroglobulin antibody in the same animal on fifteenth day of treatment was prominent. Two of twenty animals were found to be positive for both antimicrosomal and antihyroglobulin antibodies on fifteenth day of medication. In another rabbit antimicrosomal antibody was established after 7 days of treatment. All the antibody positive animals were female.

Lithium-induced histopathological alterations in the thyroid gland: As compared to the averaged 117±29 mg of the thyroid gland weight in normal adult rabbits, the mean value of the thyroid weight in the rabbits exposed to lithium carbonate medication was remarkably higher (193±23 mg in male, 222±22 mg in female, 209±43 mg in total respectively). The histopathological appearance of the gland by light microscope suggested the development of simple diffuse goitre in different stages as given in Table 2.

Table 1. The level of antithyroid antibodies in the group treated with lithium carbonate

Number	Basal	7	15	30	45	60
AMA*	1/100					
No:1						
ATA*		___	1/80	—	___	___
AMA	___	___	1/100	—	___	___
No: **2**						
ATA	___	___	1/80	—	___	___
AMA		___	1/100	—	___	___
No: 3						
ATA	> ,, ni-r–?'!:,	___	1/80	—	___	___
AMA	___	1/100	___	___	___	___
No: 4						
ATA						

*AMA: Antimicrosomal antibody
+ATA: Antithyroglobulin antibody

Table 2. The quntitative distributions of histopathological alterations in the rabbits

	Macrofollicular colloidal iterations	Microfollicular hyperplastic alterations	Degenerative alterations
Female	2	5	3
Male	1	3	6
Total	3	8	9

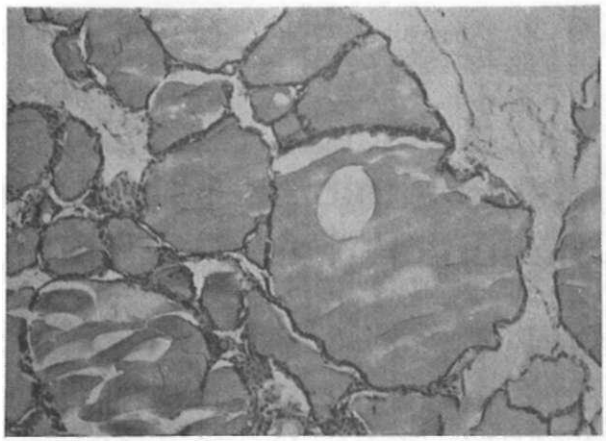

Figure 1. Histopathological appearance of thyroid gland with predominantly macro follicular colloidal alterations (HE Original magnification 41).

As presented in Figure 1, histopathological appearance resembling macro follicular colloidal goitre was established in three animals consist of two female and one male rabbits. The decrement in the epithelial heights of the follicular cells and the increment in colloidal content were the main characteristics of this type of structure. Some degenerative and empty follicles in male one, colloidal fragmentations and some epithelial hyperplasia in female ones were additional histopathological findings in three sections.

Eight rabbits covering five female and three male models revealed epithelial hyperplasia associated with macro follicular structures (Figure 2). Papillary projections into collidal content, papillary foldings and the increments, in epithelial heights were seen predominantly in all areas and in a different concentration. The decrement in peripheral follicles collidal content and the increment in the number of vacuoles were presented in six of eight rabbits. Some cystic and degenerative follicles were observed in one of the male rabbits.

In the remaining nine rabbits the follicular degeneration and the fibrosis in the sections stained by Mason's trichrom were the basic histopathological findings (Figure 3). In four of them follicular degeneration associated with the absence of intact thyroid tissue was observed. Microfollicular structures, epithelial hyperplasia, papillary projections and epithelial foldings were the additional changes in the remaining animals.

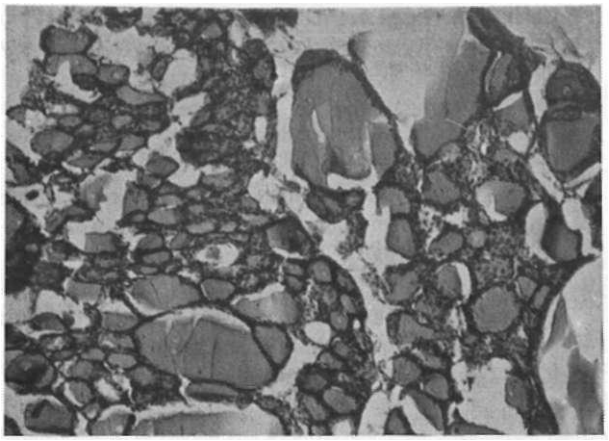

Figure 2. Histopathological appearance of thyroid gland with predominantly micro follicular hyperplastic changes (HE Original mag' ication41).

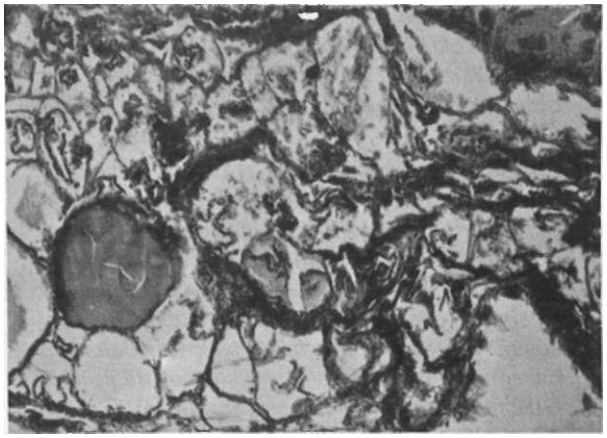

Figure 3. Histopathological appearance of thyroid gland with predominant degenerative development (Mason's trichrom. Original magnification 41).

DISCUSSION

It has been reported that diffuse or nodular goitre was observed in lithium treated patients (5). In this study we have also demonstrated the increment in the thyroid weight which has implied goitre development. There are several alternative explanations for the goitre which was induced by the action of lithium. It was noted that lithium exerts directly a growth promoter effect in FRTL-5 cell culture but we found some other histopathological alterations in the thyroid gland beside cell growth (6,8). The findings which shows lithium led reduction in the follicular epithelial height and increment in colloidal content of the medicated rats are not compatible with our results (3). We observed predominantly colloidal goiter with increased colloidal content and flattened epithelial cells just in three animal models.

Based on measurements of circulating anti thyroid antibodies, the development of autoimmune thyroiditis has been estimated to be very rare in the literature and the existence of auto immune thyroiditis in the limited time has not been reported previously as far as we know. Whereas we investigated the presence of auto immune thyroiditis by assaying anti-thyroid antibodies in the first two months. In addition, microscopic examination of the thyroid tissue did not show any histopathological appearance reminding auto immune thyroiditis. Temporary positive anti-thyroid antibody covering just a few female models might be due to non-specific tissue injury in the thyroid gland. However, the conclusion about lithium involvement in autoimmune thyroiditis development based on a marked increase in antibody titre and cellular infiltration in the thyroid gland (7,9) is not endorsed by this experiment. Species and time related changes might be responsible for the difference in data.

Polymorphic changes in some histopathological sections such as combination of involutional changes, degenerative and destructive follicular lesions with fibrosis or epithelial hyperplasia were seen. This morphological structure implies the possibility of the presence of unequal distribution of lithium carbonate in the thyroid gland. Furthermore changes in the concentration of local growth factors in the thyroid tissue might be the other responsible factors for polimorphic histopathological alterations.

As previously reported, lithium induced thyroidal dysfunction such as hypo and hyperthyroidism must be correlated with the type of histopathological changes. The presence of follicular degeneration could lead to hypothyroidism; by contrast, increased epithelial hyperplasia could be responsible for hyperthyroidism.

In conclusion, lithium induced histopathological alterations in the thyroid gland are the multifactorial process leading goitre or goitre with dysfunctions. Gender and species might be effective on progression of thyroid abnormalities. As mentioned about there is no clear-cut explanations for the pathogenesis of lithium induced thyroid abnormality. Further work based on tissue cultures and local growth factor levels could offer to understand the pathogenesis of lithium induced thyroid abnormality.

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Lityum karbonat uygulanan tavşanların tiroid bezlerindeki histopatolojik değişimler

Lityum karbonat tiroid bezinde fonksiyonel ve morfolojik değişmelere yol açan antimanic bir maddedir. Bu nedenlerdedir ki 20 mg/kg/gün dozunda 45 gün süreyle lityum carbonat uygulamasına maruz bırakılan tavşanlarda lityum karbonatın tiroid bezi üzerindeki etkileri araştırıldı. Tiroid bozukluklarınan mekanizmasının değerlendirilmesinde tiroid bezinin ışık mikroskopisi altında histopatolojik

incelenmesi ve antitiroid antikor ölçümü dikkate alındı. Tiroid bezinin görünümü değişik evrelerdeki basit diffüz guatr ile uyumluydu. Az sayıda dişi örnekte birkaç kez antitroid antikorları pozitif bulundu.

Bu veriler göstermektedir ki; 1) Lityum karbonatın tiroid bezi üzerindeki etkileri daha önce bildirilen otoimmun tiroiditis ve hypotroidiye sebep olduğuna ilişkin etkilerinde çok daha karışıktır. 2) Lityumun direkt sitotoksik etkisi genetik ve cinsiyet farklılıklarından etkileniyor gibi gözükmektedir. 3) Doku kültürü ve lokal büyüme faktörleri içeren daha ileri çalışmalar morfolojik ve fonksiyonel değişimler hakkında daha çok bilgi sağlayacaktır. [TurkJ Med Res 1995; 13(4):127-130]

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