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Observations on "Late onset disease" and Tumor Incidence in Different Strains of Laboratory Mice infected Congenitally with LCM Virus

II. Experiments with Inbred CBA/J mice

By

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With one figure and 2 tables

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In our previous work on congenitally acquired chronic infection with LCM virus (for references see (2,3)) random-bred white mice of normal immunological reactivity towards this virus were used. A mouse strain showing a delayed response to foot-pad or intracerebral (ic) infection was described in 1973 by SKINNER and KNIGHT (10), who suggested that this strain might be of value in immunopathological studies on murine LCM. A similar slow reaction had been noted in our laboratory in inbred gray CBA/J mice, which were employed in a study of "late onset disease" and tumor incidence in comparison with outbred NMRI mice of normal reactivity (13). The present paper presents results obtained with persistently infected CBA/J mice including a discussion on possible correlations between chronic LCM infection, tumor formation and occurrence of glomerulonephritis in various breeds of mice.

Material and Methods

Mice: Breeding stock of the CBA/J strain was obtained from Ivanovas & Co., Kisslegg, Allgäu. Information on the more recent history of these animals is lacking. Their reproductive efficiency is inferior to that of NMRI mice. They were fed and otherwise treated in the same way as their NMRI counterparts (13).

Virus: The unmodified strain "W" (13) was used exclusively, spleen extract from NMRI carriers serving as source of virus.

Production of congenital carriers: Strain "W" proved harmless when inoculated intracerebrally (ic) into newborn CBA/J baby mice. Such animals became virus carriers for life and females would regularly transmit the virus to

all of their embryos. No difficulty was experienced in maintaining the infection in successive generations. Congenitally infected individuals could not be distinguished from normal ones of similar age and all mice tested remained virus carriers for at least 15 months. No case of autosterilization (13) was observed.

Mouse groups, observation periods and general procedure: Batches of mice infected either congenitally or neonatally (ic) were kept under observation for different periods of time as indicated in Table 1. Thereafter, they were exsanguinated and examined for lesions. Spleen and kidney extracts from individual animals were prepared and tested quantitatively for complement-fixing (CF) antigen (13). Direct and indirect CF tests were carried out with the sera obtained from individual mice provided that the serum quantity was sufficient for both tests. This was not always the case since adult CBA mice are considerably smaller than NMRI animals and the serum yield is correspondingly less. The serological techniques used have been described in a preceding paper (13).

Results

Delayed response to ic infection with LCM virus in CBA/J mice

On numerous occasions normal adult NMRI and CBA/J mice were infected simultaneously by the cerebral route with the same virus-containing materials. Whereas NMRI mice showed the first symptoms (ruffled fur, tremors, convulsions) 5 to 8 days later depending on the amount of virus inoculated, the incubation period in CBA/J animals was invariably prolonged by about 1 day or even more. Thereafter, the course of the disease and the mortality rate were similar to those in NMRI mice. SKINNER and KNIGHT (10) had reported a delay of about 18 hours following ic infection and of 36 hours after foot-pad inoculation in their Porton 67 strain.

Since foot-pad inoculations with LCM virus strain "W" gave more or less irregular results in CBA/J mice, this mode of infection was not made much use of. Nevertheless, the few tests carried out indicated a delayed response also.

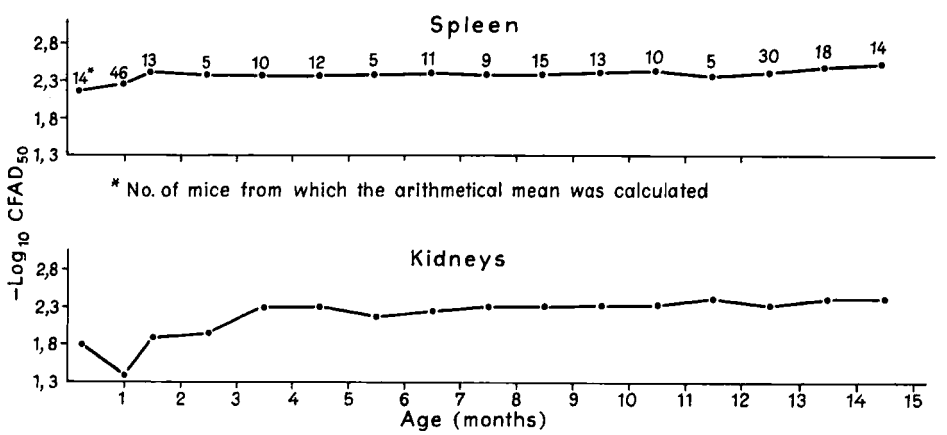

Fig. 1: CF antigen titers of spleen and kidneys at different age levels in CBA/J mice infected congenitally

Antigen content of spleens and kidneys in congenitally infected mice of different age groups

Arithmetical means of the CF antigen titers of spleens and kidneys from individual mice in different age groups are shown graphically in Fig. 1, where the figures above the spleen curve indicate the numbers of mice from which mean values were calculated for the respective age spans. These figures are also valid for the kidney curve.

The curves are similar to those obtained from congenitally infected NMRI mice (13) except that the kidney titer rose more rapidly in CBA/J animals after the low at month 1. There is no significant difference between the renal antigen titers in NMRI and CBA/J mice older than $4^1/_2$ months.

Pathological changes noted in congenitally or neonatally infected animals

The first cases of kidney disease were observed in 1972 in 5 neonatally infected CBA/J males originating from 2 different litters. All of these animals showed no obvious signs of disease intra vitam but very severe kidney changes without exudation at autopsy when examined at the age of 68 and 70 days, respectively. Antibodies could not be demonstrated in their serum by direct CF. At that time, these cases made us expect a high incidence of glomerulonephritis in persistently infected CBA/J mice.

For as yet unknown reasons, this expectation was not borne out by later experimental results. As indicated in Table 1, only 4 cases of kidney disease without exudation (3 in females and 1 in a male) were recorded in a large batch of congenitally infected animals (83 males and 143 females) sacrificed

Table 1

Tests for serum antibodies and incidence of glomerulonephritis, hemorrhagic mesenteric lymph nodes and tumors in persistently infected CBA/J mice

Mice			Positive sera		Cases of nephritis	Hemorrhagic mesenteric lymph nodes (%)	Tumor cases	
Mode of infection	Age span (days)	No.	direct CF	indirect CF			No.	type
congenital	21 - 60	45	0 / 45	0 / 36	0	0	0	
	61 - 120	16	0 / 16	0 / 11	0	13	0	
	121 - 180	17	0 / 15	0 / 10	0	40	0	
	181 - 240	25	0 / 25	0 / 16	0	71	0	
	241 - 300	32	0 / 32	0 / 21	1	85	1	multiple kidney tumors
	301 - 360	28	0 / 25	0 / 11	2	50	1	thymic
	361 - 420	40	3 / 38*	0 / 28	1	81	1	thymic
							1	mammary
	421 - 457	23	0 / 22	0 / 11	0	100	1	thymic
neonatal	72 - 120	4	no serum		0	0	0	
	121 - 180	13	0 / 13	0 / 11	0	0	0	
	181 - 223	54	0 / 52	0 / 54	0	87	0	
controls	121 - 180	27	0 / 27	0 / 27	0	0	0	
	301 - 360	13	0 / 13	0 / 13	0	0	0	

* very weak, more or less questionable reactions

at different age levels. In the 3 females with macroscopic kidney changes, but not in the male, the spleens showed a 4 to 5-fold increase in weight, whereas the kidney weights did not deviate significantly from the means for the respective age groups. In another batch of 71 neonatally infected mice consisting of 35 males and 36 females not a single case of nephritis appeared during an observation period of 223 days. In contrast to former practice (12, 14), the males were not castrated in this experiment because they are less ferocious fighters than their white counterparts.

The tumor incidence was lower than in NMRI mice. The youngest animal showing multiple kidney tumors (lymphomas?) in combination with swelling of the spleen was 288 days old. Fast-growing thymic tumors, in 2 animals coupled with 4-fold enlargement of the spleen, were seen in 3 mice 318 to 432 days old and a mammary carcinoma in one female at the age of about 1 year. This latter case, together with 3 more mammary tumors encountered in the course of 3 years in LCM-free female breeders from different generations, is evidence for the continuous presence of a mammary tumor virus in CBA/J mice with a morbidity rate far below 1 %.

Many of the older persistently infected animals showed hemorrhagic mesenteric lymph nodes which often were considerably swollen and contained about as much viral antigen as the spleen. The frequency and intensity of this peculiar lesion, always confined to the mesenteric nodes, increased with age (see Table 1). It was missing in the normal CBA/J animals recorded in this table as well as in NMRI mice, LCM-infected or not.

Another pathological condition not infrequently seen in both LCM-infected and normal CBA/J mice was a more or less severe inflammation of the anal area, often combined with moderate enlargement of the spleen, from which bacteria could not be cultivated. The cause of this condition is unknown. Few of the infected animals older than one year showed marked emaciation without any other macroscopic pathological changes.

In general, losses from "late onset disease" were much less in persistently infected CBA/J mice than in comparable NMRI animals (13).

An originally larger batch of normal CBA/J controls kept in the same building as the infected mice had to be reduced to a minimum (see Table 1) since, contrary to previous experience, some animals in several cages became accidentally infected as shown by a serological check-up. It was decided to eliminate all mice in such cages no matter whether they had developed CF antibodies or not.

Tests for serum antibodies in persistently infected CBA/J mice of different age

The results of direct and indirect CF tests with individual serums are summarized in Table 1. With the exception of 3 sera from mice older than one year which gave doubtful reactions in the direct test, the outcome was uniformly negative in both direct and indirect CF.

Numerous sera from animals of the older age groups were more or less anticomplementary in the direct CF test where cold fixation is practised (13.) In some cases this effect was so strong that conclusive results could not be obtained. It does not seem to be due to the infection with LCM virus, since some sera from old normal mice were also anticomplementary.

Discussion

Results obtained previously with congenitally infected NMRI mice (13) pointed to a correlation between the incidence of glomerulonephritis, the

concentration of viral antigen in the kidneys, and the presence of CF antibodies in the blood. This confirmed in principle earlier findings of OLDSTONE and DIXON (4), who used other methods.

The observations made with CBA/J mice described above lend further indirect support to this concept. In this case, high viral antigen titers of the kidneys in the absence of demonstrable circulating antibodies failed with very few exceptions to cause renal disease. OLDSTONE and DIXON (4) had reported that the incidence of glomerulonephritis varied considerably in different mouse strains depending on both the concentration of infectious virus in the tissues and the amount and time of appearance of LCM antibodies in the kidneys, but they did not mention a strain like CBA/J with high virus concentration in the organs and missing antibody.

It was found in this laboratory (1) that CBA/J mice infected as adults can produce LCM antibodies nearly as well as NMRI animals. However, their cellular reactivity towards this virus appears to be lowered as indicated by their delayed reaction to i. c. infection, for which lymphoid cells are held responsible. Since in congenital carriers the capacity to produce LCM antibodies is reduced as well, it may be suspected that the function of both T and B cells is impaired in such animals.

Evidence thus far available suggests that the hemorrhagic condition and gradual swelling of the mesenteric lymph nodes described above occur only in CBA/J mice infected persistently with LCM virus. Since this lesion was not seen in animals younger than 3 months, it may be a peculiar trait of "late onset disease" in this mouse strain.

Data on tumor formation and kidney disease in mice infected congenitally with LCM virus were obtained from 4 different breeds of mice used

Table 2

Incidence of glomerulonephritis and tumors in different breeds of mice infected congenitally with LCM virus

Mice		Glomerulo-nephritis	Tumors			
			leucosis			
Breed	infected or normal		Gross type ?	other type ?	mammary	pulmonary
R. I. M. R., Princeton, N. J.	infected	-*	+ (21 %)	-	-	-
	normal	-	+ (5 %)	-	-	-
C. R. I., Philadelphia, Pa.	infected	-	+ (64 %)	-	+	+
	normal	+	+ (13 %)	-	+	+
N. M. R. I., Bethesda, Md.	infected (strain "W")	+ (43 %)	-	+ (18 %)	-	-
	infected ("WCC")	+ (22 %)	-	-	-	-
	normal	+ (4 %)	-	+ (14 %)	-	-
CBA / J	infected ("W")	+ (3 %)	-	+ (3 %)	+	-

* not observed

in own work in the course of the years. For convenience they have been briefly summarized in Table 2.

In the non-inbred Princeton breed of white mice lymphatic leukemia, presumably of the GROSS type, occurred in both infected and LCM-free animals with an incidence of 21 and 5 %, respectively (11). Other tumors and glomerulonephritis were not recorded in this mouse strain either in experimental animals or in the Princeton breeding stock, whose health was closely checked.

The situation was different in white CRI mice, the ancestors of which were obtained from the Cancer Research Institute in Philadelphia, Pa. in 1955. Several kinds of tumors were recorded in this breed (14); leucosis (probably GROSS type) and mammary carcinoma, both with relatively high incidence; pulmonary carcinomas or adenomas (2 to 3 times less frequently than the tumors just mentioned); adenomas and hemangiomas of the liver (rarely). A viral etiology is established for the first two tumor varieties only. These were never seen simultaneously in the same female. The incidence of leucosis amounted to 64 % in CRI mice infected congenitally with LCM virus and 13 % in LCM-free controls (12). It is possible, however, that the result was modified to some extent by linebreeding. Whether the low malignancy of leucosis in LCM-infected animals was caused by an interaction between LCM virus and the leucosis agent or by linebreeding is not known.

Many animals showing the severe exudative form of glomerulonephritis were delivered from the LCM-free CRI breeding stock colony to the author's laboratory for examination. The affected mice were usually older than 4 months. Breeders were discarded and replaced by young stock at the age of 6—7 months. Nephritis also occurred with considerable frequency in a large LCM-free batch of CRI mice kept under life-long observation for experimental purposes (14). Since the disease had nearly reached epidemic proportions and its pathogenesis was not yet known at that time, transmission experiments were carried out using as recipients normal NMRI mice, in which this syndrome had not been observed. It is now no longer surprising that this attempt failed. No cases of glomerulonephritis were recorded in CRI carriers of LCM virus either in tumor experiments or in LCM-infected breeding stock (12).

According to present knowledge it seems likely that an immunological reaction to the leukemia virus (6) was responsible for the glomerulonephritis in LCM-free CRI mice, although a possible role played by persisting mammary tumor virus cannot be entirely ignored. In LCM-infected CRI mice the immune reaction leading to kidney disease was probably prevented by an immunosuppressive action of persisting LCM virus.

Another situation was encountered in NMRI mice, in which a leucosis agent presumably different from GROSS leukemia virus seems to exist (13). Typical cases of kidney disease were rare in LCM-free animals of this breed (see Table 2) but occurred at an overall rate of 43 % in congenital carriers of strain "W" of LCM virus. In this system, the immune response to leucosis virus appears to have been weaker than in CRI mice, judging from the lower incidence of glomerulonephritis in LCM-free animals. There was no concrete evidence of tumor inhibition in mice carrying strain "W", especially if one considers both the suspicious cases and the definite ones (13). This was different in 33 congenital carriers of modified "WCC" virus (13), all of which failed to show tumorous growths. However, this observation needs to be extended to a larger number of animals.

The low rates of glomerulonephritis and tumors in CBA/J mice (see Table 2) and the lack of an adequate number of LCM-free controls of suitable age do not allow conclusions as to a possible interaction between LCM and tumor viruses in this mouse strain.

That murine leukemia virus can be activated by LCM virus was shown by OLDSTONE et al. (5), who reported increased formation of GROSS leukemia antigen, obviously independent of genetic factors, in LCM-infected mice and cell cultures. In recent work by SKINNER (9) a much higher incidence of lymphoid tumors (in the absence of glomerulonephritis) was found in Pirbright P mice infected congenitally with LCM virus than in genetically identical LCM-free controls (61 vs. 2.5 %). A stimulating effect of LCM virus on the formation of certain lymphoid tumors in mice can now no longer be doubted. The basic mechanism, however, requires further study. This also applies to the great differences in tumor malignancy observed with various systems (11,12,9).

PADNOS and MOLOMUT (7), working with the somewhat atypical LCM (M-P) virus, observed an inhibitory action of this strain upon mouse tumors and oncogenic viruses. According to these authors, this effect appears to be mediated via induced serum interferon during 2 to 5 days, followed by an immune reaction.

The histopathology in LCM carrier mice is complicated by immunoproliferative changes (plasmacytomas) associated with the chronic LCM infection. They are most conspicuous in gnotobiotic HAAS strain mice (8) and, in contrast to leukemia, respond to immunosuppressive therapy. According to present knowledge, hardly any strain of laboratory mice is free of vertically transmitted leucosis virus (8). The interaction of different leucosis agents with persisting LCM virus appears to vary as suggested by the experimental data discussed above. It is evident that the persistence of different vertically transmitted viruses in the same individual offers intriguing problems and may have practical implications in the cancer field.

For further references and comments the reader is referred to recent reviews (2,3).

Summary

Adult CBA/J mice regularly showed a delayed response to intracerebral inoculation with LCM virus indicating an impaired cellular reactivity toward this agent.

Viral antigen titers of spleens and kidneys were about equally high in congenitally infected CBA/J and NMRI mice sacrificed at different age levels, but the former animals, unlike those of the NMRI strain, failed to develop serum antibodies demonstrable either by direct or by indirect complement fixation.

This result, together with the rare occurrence of glomerulonephritis in CBA/J carriers supports the concept that antibodies are involved in the pathogenesis of kidney disease in mouse strains with a high incidence of nephritis, for instance, NMRI carriers.

Old CBA/J mice persistently infected with LCM virus frequently showed swollen and hemorrhagic mesenteric lymph nodes, a peculiar lesion not seen in uninfected animals of this breed or in NMRI mice of similar age, infected or normal.

Thymic, renal and mammary tumors occurred at a very low rate in old CBA/J carriers.

Possible correlations betweeen chronic LCM infection, tumor incidence and frequency of glomerulonephritis are discussed making reference to previous own work with different mouse strains and that of other investigators.

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Zusammenfassung

Beobachtungen über „Späterkrankungen" und Tumorauftreten bei unterschiedlichen, congenital mit LCM-Virus infizierten Labormäusestämmen

II. Versuche mit Inzucht CBA/J-Mäusen

Erwachsene CBA/J-Mäuse erkrankten nach cerebraler Injektion von LCM-Virus regelmäßig verspätet, was auf eine verminderte zelluläre Reaktionsfähigkeit gegenüber diesem Erreger hinweist.

Der Gehalt der Milz und Nieren an Virusantigen war bei congenital infizierten CBA/J-Mäusen verschiedener Altersstufen ungefähr gleich hoch wie bei altersmäßig vergleichbaren Virusträgern des NMRI-Stammes, doch bildeten die ersteren im Gegensatz zu NMRI-Tieren keine, weder durch direkte noch durch indirekte Komplementbindung nachweisbaren Serumantikörper.

Dieses Ergebnis, im Verein mit dem seltenen Vorkommen von Glomerulonephritis bei CBA/J-Virusträgern, stützt die Auffassung, daß Antikörper an der Pathogenese der Nierenerkrankung bei solchen Mäusestämmen beteiligt sind, die eine hohe Nephritisquote aufweisen, so z. B. bei congenital infizierten NMRI-Mäusen.

Ältere persistent infizierte CBA/J-Tiere zeigten häufig geschwollene und hämorrhagische Darmlymphknoten, eine eigenartige Veränderung, die weder bei nicht infizierten Mäusen dieser Zucht, noch bei infizierten oder normalen NMRI-Tieren beobachtet wurde.

Bei alten CBA/J-Virusträgern wurden Thymus-, Nieren- und Mammatumoren, jedoch nur in sehr geringer Zahl festgestellt.

Mögliche Zusammenhänge zwischen chronischer LCM-Infektion, Tumorbildung und Häufigkeit von Glomerulonephritis werden an Hand von früheren eigenen Versuchsergebnissen sowie von Befunden anderer Autoren diskutiert.

Résumé

Observations sur des «maladies retardées» et l'apparition de tumeurs chez différentes souches de souris de laboratoire infectées congénitalement avec un virus LCM

II. Essais avec une souche consanguine de souris CBA/J

Des souris CBA/J adultes tombèrent malades avec retard après une injection cérébrale de virus LCM, ce qui montre une capacité de réaction cellulaire diminuée vis-à-vis de cet agent.

Le taux d'antigène viral de la rate et des reins fut à peu près le même chez des souris CBA/J d'âges différents congénitalement infectées que chez des animaux de souche NMRI d'âge comparable porteurs du virus; les premières au contraire des souris NMRI ne présentèrent aucun anticorps sérique à la réaction de fixation du complément direct et indirect.

Ce résultat, en accord avec l'apparition peu fréquente de glomerulonéphrite chez les porteurs CBA/J de virus, appuie la thèse disant que les anticorps participent à la pathogénèse des affections rénales chez ces souches de souris qui présentent une forte proportion de néphrites comme c'est le cas par exemple chez des souris NMRI infectées congénitalement. Des animaux CBA/J, plus âgés, chroniquement infectés, présentèrent fréquemment des ganglions intestinaux grossis et hémorragiques, lésion particulière qui n'a été observée ni chez les souris non infectées de cet élevage ni chez les animaux NMRI infectés ou normaux.

Un très faible nombre de tumeurs du thymus, des reins et de la mamelle fut constaté chez des CBA/J âgés, porteurs du virus. On discute les relations possibles entre une infection LCM chronique, la formation de tumeur et la fréquence des glomerulonéphrites en considérant les résultats précédemment acquis et les données d'autres auteurs.

Resumen

Observaciones sobre "enfermedades tardías" y aparición de tumores en varias estirpes de ratones de laboratorio, infectados por vía congénita con virus LCM

II. Ensayos con ratones CBA/J de consanguinidad estrecha

Ratones adultos CBA/J enfermaban de forma regular retardada, tras inyección intracerebral de virus LCM, lo que señala hacia una reactividad celular disminuida frente a este agente etiológico.

El contenido esplénico y renal en antígeno virósico era casi igual de elevado en ratones CBA/J infectados congénitamente, de edades diversas, que en los portadores de virus de la estirpe NMRI de edades equivalentes, ahora bien, los primeros no formaban seroanticuerpos en contraste con los animales NMRI que pudieran ser identificados mediante fijación directa o indirecta del complemento.

Este resultado, unido a la presencia rara de glomérulonefritis en portadores de virus CBA/J, sustenta el punto de vista que los anticuerpos participan en la patogenia de las nefropatías en aquellas estirpes murinas que evidencian una tasa elevada de nefritis, como p. ej. en los ratones NMRI infectados por vía congénita.

Animales adultos CBA/J, infectados de modo persistente, solían presentar ganglios linfáticos mesentéricos tumefactos y hemorrágicos, una modificación singular no observada ni en los ratones no infectados de esta progenie ni en los animales NMRI infectados o normales.

En portadores adultos de virus CBA/J se ubicaron tumores en timo, riñón y mama, aunque en cantidad muy escasa.

Se discuten las interrelaciones posibles entre infección crónica LCM, resultados experimentales propios anteriores y de hallazgos de otros autores.

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