The Epidemiology of Avian Lymphoid Leukosis

L. B. Crittenden

United States Department of Agriculture, ARS Animal Physiology and Genetics Institute, Beltsville, Maryland 20705

Summary

Avian lymphoid leukemia can be induced by lymphoid leukemia viruses belonging to Subgroups A, B, C, and D. The endogenous virus of the chicken (Rous-associated virus type 0) belongs to Subgroup E and has little, if any, potential for inducing lymphoid leukemia. Nearly all chicken flocks are infected with Subgroup A lymphoid leukemia virus. This virus can be transmitted from dam to offspring or by contact with infected birds. Early infection, either by congenital means, or soon after hatching, leads to the highest incidence of lymphoid leukemia. Maternal antibody or genetic resistance to infection delays or prevents infection, leading to a lower incidence of disease. In flocks segregating for genetic resistance to infection, continued infection is maintained through dynamic interactions between genetic resistance, acquired or maternal antibody, and virus infection. Expression of endogenous viral information is controlled by dominant genes, but spontaneously produced Rous-associated virus type 0 can spread through a susceptible flock and be transmitted like an exogenous virus.

Introduction

LL² is the most common naturally occurring neoplasm of the fowl associated with the avian L-S group of viruses. It is a lymphocytic lymphoma arising from malignant lymphocytes of bursal origin. Infection at an early age induces the formation of foci of malignant lymphoblasts in individual bursal follicles. After sexual maturity, the malignant lymphocytes migrate to other visceral organs and proliferate to form tumors (1, 14).

Biology of the L-S Virus Group

The avian L-S virus group is typical of the C-type animal RNA tumor viruses and can be subclassified as shown in Table 1. These viruses are classified into 7 subgroups (A through G) on the basis of the viral envelope properties of interference, antigenicity, and host range (8, 10). Each subgroup has also been divided into sarcoma viruses that induce rapid transformation in cell culture and in vivo and leukemia viruses that rarely transform cell cultures but may induce neoplasms in vivo only after a long latent period (14). The sarcoma viruses have been further divided into those that require a helper leukemia virus for infectivity and those that do not (19).

Sarcomas rarely occur in nature, but the RSV's are very useful in studies of LLV's because they share envelope characteristics with the associated LLV of the same subgroup (19). Their use allows rapid assays for genetic resistance to infection and for the occurrence of neutralizing antibodies.

The only known endogenous virus of the chicken (RAV-0) belongs to Subgroup E. It is a typical L-S virus but has some unique characteristics (7, 20).

Prevalence of Infection and Disease in Chicken Flocks

It has long been recognized that LLV infection is widespread, because antibodies to RSV have been found in most chicken flocks (9, 15, 17). Transmission from bird to bird is by contact or by congenital infection from the dam (1, 16). Virus-infected males do not transmit virus to their progeny (16). Congenital infection is the most important means of perpetuating infection, because birds infected as embryos often became immunologically tolerant to LLV and remain viremic throughout their lifetimes (16).

Surveys of subgroup distribution in commercial chickens indicate that Subgroup A is the most prevalent, while Subgroup B infection occurs rarely and usually in conjunction with Subgroup A infection. Subgroup C and D virus infection is very rare (3, 14). Experimental studies have shown that all 4 subgroups induce LL (H. G. Purchase and W. Okazaki, in preparation). Surveys have not been conducted to determine the frequency of infection with RAV-0. Spontaneous occurrence or infection with RAV-0 has little if any effect on the incidence of LL before the chicken is 2 years old and beyond its commercial usefulness (H. G. Purchase, W. Okazaki, L. B. Crittenden, and J. V. Motta, in preparation). Naturally occurring Subgroup F and G virus infection is thought to be confined entirely to the pheasant (10).

Chronic morbidity and mortality in adult chickens occurs in Subgroup A virus-infected flocks. The disease rarely occurs before sexual maturity, and only occasionally does the incidence go over 10% in the 1st 2 years of life. Occasional flocks do suffer severe losses (14). The fact that inoculation of LLV induces LL and that flocks free of LLV infection rarely, if ever, have cases of LL strongly supports the etiological relationship between the virus and the disease (1, 14, 16).
Table 1

Subclassification of viruses of the avian L-S group

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Helper-independent</th>
<th>Helper-dependent</th>
<th>Leukosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SR-RSV-A PRC2-A</td>
<td>BH-RSV(RAV-1)</td>
<td>RAV-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BH-RSV(RPL-12)</td>
<td>RPL-12</td>
</tr>
<tr>
<td>B</td>
<td>SR-RSV-B PRC2-B</td>
<td>BH-RSV(RAV-2)</td>
<td>RAV-2</td>
</tr>
<tr>
<td>C</td>
<td>B-77 PR-RSV-C</td>
<td>BH-RSV(RAV-7)</td>
<td>RAV-7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BH-RSV(RAV-49)</td>
<td>RAV-49</td>
</tr>
<tr>
<td>D</td>
<td>SR-RSV-D CZ-RSV-D</td>
<td>BH-RSV(RAV-50)</td>
<td>RAV-50</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>BH-RSV(RAV-0)</td>
<td>RAV-0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BH-RSV(RAV-60)</td>
<td>RAV-60</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>BH-RSV(RAV-61)</td>
<td>RAV-61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BH-RSV(RPV)</td>
<td>RPV</td>
</tr>
<tr>
<td>G</td>
<td></td>
<td>BH-RSV(GPV)</td>
<td>GPV</td>
</tr>
</tbody>
</table>

This paper considers the known epidemiological factors affecting infection and LL induction by LLV of Subgroup A, because this is the most prevalent virus associated with the occurrence of LL in chicken flocks. Furthermore, enough information is available to develop an epidemiological model of virus transmission and disease. The transmission of endogenous viral information and its expression will also be discussed, even though its influence on the incidence of LL is questionable.

Factors Affecting Resistance to Subgroup A Virus Infection

Three major factors limit Subgroup A virus infection. (a) Maternal neutralizing antibody reduces susceptibility of the chick to infection for the first 3 to 7 weeks of life. The titer of antibody in the dam’s serum is related to the persistence of maternal antibody in the chick (14, 15, 21). (b) Acquired neutralizing antibody limits reinfection and persists for long periods in the dam so that maternal antibody is passed on to the chick through her reproductive lifetime (16, 17). (c) A single autosomal recessive gene controls resistance to infection by Subgroup A LLV. This resistance is so complete that resistant chickens seldom develop antibodies to Subgroup A virus (5, 6).

These mechanisms of resistance to infection are specific to the viral envelope and therefore are highly subgroup specific (5).

Factors Affecting Resistance to LL Development

Prevention of infection is a major factor in resistance to LL development, but several additional factors reduce the probability of the occurrence of LL after the bird becomes infected: (a) the incidence of LL goes down quickly if infection by natural routes occurs after the first few weeks of age

(2, 14); (b) acquired immunity to LL development may occur but has not been well documented; (c) there are well-established genetic differences in susceptibility to LL development in chickens that are equally susceptible to virus infection (5, 6); and (d) the bursa of Fabricius is required as a target organ for the initial transformation to lymphoma cells (1, 14).

Resistance to tumor development after infection is largely related to new properties of cells after the introduction of the viral genetic information. Therefore, this type of resistance is not related to the viral envelope properties and is not subgroup specific.

Epidemiological Model for Subgroup A Virus Infection and Development of LL

The facts presented in the preceding sections justify 3 major assumptions: (a) very early or congenital infection leads to a high incidence of LL; (b) resistance due to genes or maternal antibody prevents or delays virus infection; and (c) dams genetically resistant to LLV infection do not develop antibody and thus cannot protect their progeny, which are genetically susceptible if they acquire a dominant gene for susceptibility from their sire (4).

Based on the above assumptions, dams may be classified into 5 major groups (Table 2). Two types have been found to shed virus into their eggs. (a) Those that are genetically susceptible, viremic, and lack antibody (SV-A-) consistently shed virus and are thought to be immunologically tolerant (16). (b) Some of those that are genetically susceptible and nonviremic have acquired antibody (SV-A+) also have virus in some tissues and shed virus but, usually, less regularly (16). Three types do not shed virus: (a) some of those that are genetically susceptible, virus free, and have acquired antibody (SV-A+) (16); (b) those that are susceptible but virus free and antibody negative (SV-A-); and (c) those which are resistant and are virus free and antibody negative (RV-A-). SV-A- adults represent birds that have never been infected and occur at a low frequency in most chicken flocks (1, 13).

Day-old chicks of the same types occur, but their neutralizing antibody is maternal in origin. Two additional types can also occur, those which are resistant to infection but...
receive maternal antibody from their susceptible dam (RV-Av) and those which are susceptible but are congenitally infected by their antibody-positive dams (SV-Av). These birds would have maternal antibody, but their cells could have a latent infection with LLV.

Table 2 presents the types of progeny which can be produced by the 5 types of dams. Each is characterized by an estimated probability of getting LL based on an increased probability of early infection.

Theoretically, the most desirable type of flock would be made up of individuals that are homozygous recessive for the gene for virus resistance (RV-A-v) (5). Such a flock would automatically be freed of virus infection. However, since genetic resistance to infection is subgroup specific, these chickens could become infected with other virus subgroups and might be particularly susceptible to LL development because there had been no opportunity for natural selection for resistance at that level.

A flock that is genetically susceptible could also have a low rate of LL if dams were consistently infected after their age-related susceptibility had passed but before they produced progeny. Most dams in such a flock would be SV-A- or SVvA, and maternal antibody would delay infection in the SV-A- chicks. A number of chicks do become congenitally infected from the SV-A- dams, but the rate of infection varies from dam to dam and flock to flock (13, 16). If such a flock produced only SV Av chicks, virus would be eradicated, and the chicks would become susceptible to horizontal reinfection from outside sources at an early age. Early infection might be prevented by artificial infection during the growing period which would induce high levels of antibody in the dams during the reproductive period. However, it is not known how many dams infected in this way shed virus.

Studies of susceptible commercial flocks indicate that the rate of virus shedding seldom goes over 10%, so that the proportion of SV-A- and SVvA- chicks is generally low (3, 11, 15-17). However, if a flock were kept free of virus infection until its reproductive age and it then became infected, a transient viremia could spread through the flock causing a temporary high rate of congenital transmission and a subsequent high level of LL.

Vertical transmission and reinfection of very young chicks could become established in a flock segregating for susceptibility to infection by Subgroup A viruses. The frequency of the resistant gene would determine the proportion of dams which are resistant and therefore RV-A-v. These dams would not acquire antibody, even after artificial virus exposure, and when mated to sires carrying dominant genes for susceptibility, would produce SV-A- chicks which are very susceptible to early infection, a proportion becoming tolerant and viremic (4, 16). For this reason it has been suggested that a completely resistant flock or a completely susceptible flock is likely to have a lower incidence of LL than a segregating flock in which viremia can easily be maintained and reestablished (H. C. Löliger and D. Harris, personal communication).

Control of Endogenous Virus Expression

Considerable evidence has accumulated suggesting that many or perhaps all chickens have enough viral genetic material for partial or complete virus expression incorporated into their genomes (18). Payne and Chubb (12) first showed that an autosomal dominant gene controlled the expression of viral group-specific antigen in the absence of virus production. We have shown that the spontaneous production of a complete infectious endogenous virus (RAV-0) is also under the control of dominant genes (Ref. 6; L. B. Crittenden, unpublished). While it has been assumed that these genes function by controlling the expression of the proviral genes, the possibility that they carry structural proviral information has not been eliminated.

Since the occurrence of partial or complete virus expression is controlled by autosomal dominant genes, both the sire and the dam contribute equally to virus transmission. Now we know that RAV-0 can infect susceptible non-virus-producing chickens and behave as an exogenous virus (L. B. Crittenden, in preparation). As an exogenous virus, RAV-0 infection and immunity appears to follow the epidemiological model presented for Subgroup A viruses, except that it has little or no potential for inducing LL.

Conclusions

The epidemiological principles of Subgroup A virus transmission, antibody production, and genetic resistance as they relate to the development of LL are well understood. However, not enough flocks have been studied in detail to establish even rough quantitative estimates of the effects of the various factors on the flock incidence of disease. It is recognized that incidence can be influenced by the genetic makeup of the flock in regard to both resistance to infection and LL development as it relates to epidemiological parameters. Other unrecognized factors also must influence the rate of infection and disease.

Endogenous virus expression is initially controlled by dominant genes, but RAV-0, when spontaneously produced, may then infect susceptible birds and behave like an exogenous virus. Endogenous virus expression has little or no effect on the occurrence of LL in chickens.

Acknowledgments

The author gratefully acknowledges the help of B. R. Burmester, H. G. Purchase, W. Okazaki, R. A. Weiss, and many others who helped formulate the ideas presented through continuing discussion.

References

6. Crittenden, L. B., Purchase, H. G., Solomon, J. J., Okazaki, W., and...


The Epidemiology of Avian Lymphoid Leukosis

L. B. Crittenden


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/36/2_Part_2/570

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.