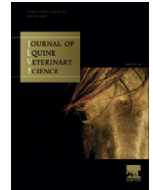




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Original Research

Various Circumstances Regarding Initial Allergen Exposure and Their Influence on Development of Insect Bite Hypersensitivity in Horses

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ABSTRACT

Insect bite hypersensitivity (IBH), an allergic reaction to the saliva of *Culicoides*, occurs in all horse breeds and is a severe problem. In this study, we aimed at exploring whether exterior conditions, such as duration of allergenic exposure during the first summer and age of the horses at the time of import, influence the development of IBH. Additionally, data were analyzed regarding the period IBH started after birth and after import. Datasets for 582 horses were collected. The horses were locally born Icelandic horses and horses of other breeds with IBH, as well as imported Icelandic horses, both affected and nonaffected. For locally born horses, time of birth and duration of allergen exposure during the first summer had no influence on the prevalence of IBH. The disease started mostly in their third year of life. The majority of the imported horses affected caught IBH during their first year in Central Europe. Older imported horses seemed to develop IBH quicker than younger animals. Animals imported in their first winter are exposed to the allergen when they are at least 7 months old. They experienced approximately the same low risk of developing IBH as locally bred horses. The risk of IBH increased with the horses' age at import. From our data, we conclude that the period to develop successful immune tolerance goes beyond the perinatal phase and is longer than formerly supposed.

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1. Introduction

The global occurrence of insect bite hypersensitivity (IBH) in all horse breeds is 3%–5% [1], whereas 1.5%–8.2 % of Icelandic horses born in Central Europe develop IBH [2,3]. A much higher prevalence ranging from 26% to 72% has been documented for horses imported from Iceland [3–5]. The bite of *Culicoides* and the resulting allergic reaction are viewed as the main causes [6,7]. Determining influencing factors is interesting, as not all of imported and locally born horses are affected by the disease. There was no difference in the prevalence of IBH relative to gender or color of the horse [3,8]. However, it has been reported that genetic factors are involved in immunological diseases such as IBH [9–11] and recurrent airways obstruction in horses [12]. The disease is influenced by certain environmental factors such as altitude

and wind conditions [5]. In some countries, including Iceland, where *Culicoides* are absent, IBH does not occur [1]. It is assumed that the earliest possible exposure to the allergen (prenatal or shortly postnatal) is essential for the development of immune tolerance [5]. Horses imported from Iceland are not exposed to the allergen at this age, which may explain the higher prevalence in imported horses [13].

The objective of our research was to examine the influence of certain factors during the initial exposure to the allergen. These factors are duration of allergen exposure during the first summer of locally born animals and age at time of import.

Because a higher risk for IBH could be expected from a sudden and intensive exposure to the allergen, the date of birth should be of some influence. Thus, foals that were born in Central Europe early in the year and experience a great exposure to the allergen could bear a higher risk of developing the disease than foals that were born later in the year. The immune response of younger horses to the allergen is assumed to be different from those of older

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horses [13], so the age at import possibly has an effect on the development of IBH.

Solutions to these issues would be of practical value for the animals as well as for their owners and would also allow conclusions on underlying immunological processes. Data were also analyzed concerning time elapsed since birth and import until onset of IBH.

2. Material and Methodology

2.1. Definition, Collecting of Data

The symptoms of IBH are pruritus, swelling, loss of mane and tail hairs to varying extents, alopecia, dandruff, excoriation, and open wounds. The most commonly affected areas are crest, tail, head, abdominal seam, and croup [8,14]. Depending on the severity, more symptoms can be found and more parts of the body are afflicted. Because of the seasonal occurrence of IBH only in the warmer times of the year, diagnosis can be verified fairly easily. Data were collected through questionnaires. The answers given by the owners of individual horses were discussed over telephone, whereas larger operations were visited personally. IBH diagnosis was based on clinical signs. The animals were defined as affected when one or more of the aforementioned symptoms were present in addition to pruritus only between March and November. Often, a veterinarian contributed to diagnosis, but seldom it was possible to regard the results of special examination (serological test for Immunoglobulin E (IgE) level, functional in vitro test, biopsy, intradermal test). However, the owners of the bigger operations mostly preferred to judge and treat their own horses. This is certainly a limitation to the quality of data.

On the other side, collecting data with help of the owners was imperative, as symptoms can be influenced by successful therapy and may also vary without treatment from one year to the next [15]. For these reasons, evaluation by outsiders could be useless. The severity of IBH was not taken into account, but merely its presence (yes/no). The results of this study were more clearly defined without considering the severity of the disease.

Imported horses were defined as not affected when the time of import was more than 5 years before the commencement of this study and no signs of IBH had developed so far. Because the results of this survey and other references [9] show that an average of 90% of the affected horses developed IBH within 5 years after import [16], this time span is a justifiable working basis.

2.2. Locally Born Horses

Horses “locally born” are defined as animals bred in continental Europe: mainly in Germany, few horses in The Netherlands, Switzerland, and Austria. They are classified as “other breeds” (breeds except Icelandic horses) and Icelandic horses. The 38 horses of “other breeds” came from 36 different stables and locations and contained a range of breeds. The 75 locally born Icelandic horses came from 55 different operations and locations. All stables kept affected and nonaffected animals.

We differentiated between “other breeds” and Icelandic horses because livestock breeding conditions differ from

one another and therefore different control groups had to be chosen. Because Icelandic horses usually are bred in the herd, foals are born later, and the fact that they are commonly kept outside throughout the whole year may influence the occurrence of IBH.

The distribution of birth dates through breeding season was determined. The data of one of the breeding associations operating mainly in Germany was used as normal distribution (as shown in Table 1). These data were collected from 577 Icelandic horses and 309 horses of other breeds during the period of 4 years. According to literature (see Introduction), the percentage of animals affected with IBH within the control group is approximately 6%. This means that an estimated 94% of all horses in the control group can be classified as not affected with IBH.

2.3. Imported Horses

Two data entry groups were distinguished: The “total number of imported horses” (469 horses) came from 86 stables and locations. IBH was found in all of them. Within this entry group the date of onset of IBH was known of 152 horses. For each location, data for 1–40 horses were collected and evaluated concerning the period between import and onset of IBH.

To depict the prevalence of IBH in the different age groups of horses, animals were chosen from stables where all imported horses or all horses of one age group (affected and nonaffected) could be recorded (400 horses). The animals came from 42 stables where IBH occurred in all age groups. Among the reported animals, a larger number of weanlings were found to be imported at the age of 3–9 months during their first winter. These foals were documented separately, as it soon became apparent that they stood out concerning the development of IBH. Therefore, the imported yearlings were divided into foals imported until February (“≤ Feb”) and foals imported from March until their second December (“after March 1”).

2.4. Statistical Analysis

The probabilities of infestation with IBH were compared by means of two binomial distributions. The test statistic Z

Table 1

Distribution of births through the season for horses with IBH; horses of a breeding association used as control group

Months	Other Breeds				Icelandic Horses			
	Horses with IBH		Breeding Association		Icelandic Horses with IBH		Breeding Association	
	n	%	n	%	n	%	n	%
<March	3	9	24	7	—	—	—	—
March	8	24	56	17	—	—	—	—
April	8	24	69	21	6	8	46	8
May	10	30	90	28	37	51	242	42
June	1	3	52	16	20	27	202	35
July	3	9	26	8	5	7	58	10
August	—	—	9	3	3	4	23	4
≥September	—	—	—	—	2	3	6	1
Total	33	100	326	100	73	100	577	100

IBH, insect bite hypersensitivity.

for groups n1 and n2 approximately features standard deviation. The null hypothesis means that probabilities of infestation are equal for the groups. If test statistic Z exceeds a predefined threshold value, the null hypothesis is rejected, meaning that the probability of infestation varies between the tested groups.

With this method, we assured a difference of probabilities for IBH rates between two study groups. The study groups were investigated with respect to distribution of births through the season, age at import, and period between allergen exposure and onset of IBH.

3. Results

3.1. Seasonal Distribution of Births

As shown in Table 1, the “other breeds” as well as the Icelandic horses (total 106 horses) do not demonstrate any major percentage deviations compared with the control groups (breeding association). Horses with IBH were not born earlier or later in the year than animals in the control groups. Thus, there was no correlation between time of birth and prevalence of IBH.

The probability of infestation within the first and the second half (March until June/July until September) of the breeding season was tested for both study and control group comparing the binomial distributions. For the Icelandic horses, we determined $P = .378$, and for horses of other breeds, $P = .386$. These high P values may indicate that the distributions of births in study and control groups were similar.

3.2. Period Between Exposure to the Allergen and Onset of IBH

3.2.1. Period Between Birth and Onset of IBH

Figure 1 shows that IBH most commonly occurs during the third year. Typically, the first symptoms only start to appear at the age of 14–16 months. The tendency of the results of Icelandic horses and those of other breeds was similar (Fig. 1). 61% of the “other breeds” and 74% of the Icelandic horses developed IBH within 4 years after birth. Between the 5th and the 8th year, IBH occurred at 33%

within the “other breeds” and at 17% within the Icelandic horses.

3.2.2. Period Between Import and Onset of IBH

Figure 1 shows the highest number of IBH occurred during the year of importation and during the following year (42%). In all, 11% of them were affected by IBH in the first summer. Most of these horses were imported from Iceland between spring and summer and contracted IBH within weeks or a few months. It is of practical use to know that within the period of 3 years, 82% of the horses developed IBH.

3.2.3. Statistical Assessment

The imported horses reacted quicker (most incidences at 1 year after exposure), developing IBH after allergen exposure than locally born horses (most incidences at 3 years after exposure). The probabilities for the IBH rates in the case of 1 year after exposure were compared by means of two binomial distributions and showed a significant difference ($P = .0146$) between locally born and imported Icelandic horses. In case of 3 years after exposure, the difference of probabilities showed a P value of .0023.

3.3. Age at Import

The influence of the age at import on the prevalence of IBH is shown in Table 2. Horses aged about 4–10 months, imported in their first winter before their second summer, had an IBH rate of 6%. About half of the horses imported at the age of 6 years got IBH. Horses imported when aged ≥ 12 years had a rate of 80%. The risk for IBH was found to increase continuously with age at import (Fig. 2).

For statistical analysis, the prevalence of younger age groups was compared with those of older age groups (Table 3). The difference between the age groups regarding prevalence is significant ($P < .001$). Even when low-risk weanlings (“ $\leq$ February”) were excluded from the analysis (last 4 lines in Table 3), the differences between these age groups were predominantly significant. This means that the different rates of IBH between older age groups are confirmed.

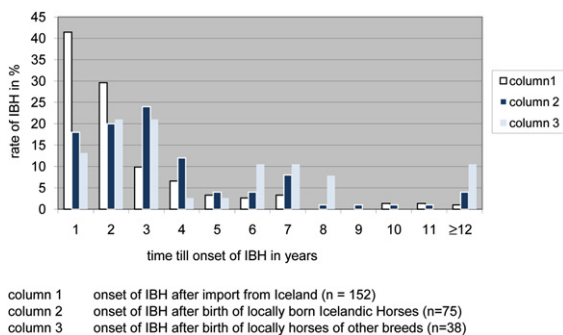


Fig. 1. Period between exposure to the allergen (birth/import) and onset of insect bite hypersensitivity (IBH). Column 1: onset of IBH after import from Iceland ($n = 152$). Column 2: onset of IBH after birth of locally born Icelandic horses ($n = 75$). Column 3: onset of IBH after birth of locally horses of other breeds ($n = 38$).

Table 2

Age at import: prevalence of IBH in the different age groups (Icelandic horses)

Age	IBH n	Not IBH n	Total n	IBH %
$\leq$ February	11	171	182	6
After March 1	5	24	29	17
2	2	7	9	22
3	7	10	17	41
4	6	16	22	27
5	13	21	34	38
6	21	19	40	53
7	21	10	31	68
8	12	7	19	63
9	2	1	3	67
10	5	0	5	100
11	3	1	4	75
≥ 12	4	1	5	80
Total	112	288	400	

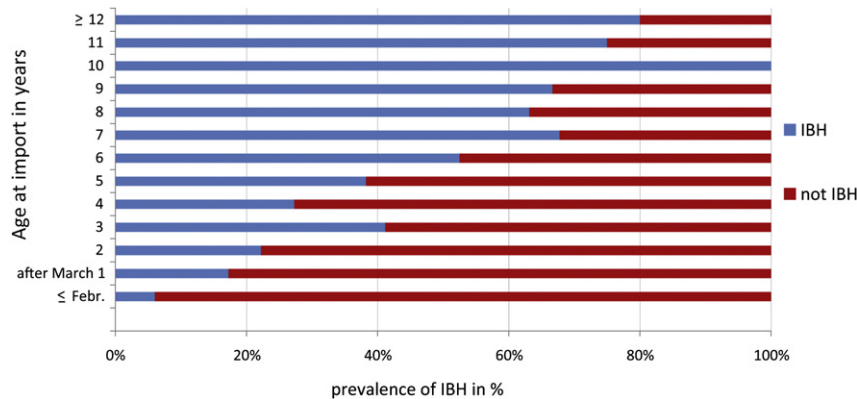


Fig. 2. Age at import. Prevalence of IBH in different age groups, Icelandic horses.

3.4. Influence of Import Age on the Period Between Import and Onset of IBH

Data in Table 4 show an influence of age at import. The over seven-year-old imported animals contracted IBH earlier than horses imported at a young age. However, this discrepancy could be coincidental in view of the small number of animals.

4. Discussion

Exposure of the organism to the allergen as early as possible is assumed to be one important factor for developing immunological tolerance. As found in humans and some laboratory species, modulations of the immune system prenatal and early postnatal have decisive influence on the development of later allergies [17]. In contrast to locally born horses, imported horses do not experience the allergen in their prenatal and early postnatal life. This is seen as the root cause for the significant higher prevalence in imported animals [5,13]. Another possible reason for this fact is the higher endoparasitic burden of horses in Iceland

compared with those kept in continental Europe [18]; one study has discussed immunological network associated with endoparasitic burden [13].

The different durations of contact of locally bred foals with the allergen during the first summer depend on whether the birthdate is early or late. Also, the way of being exposed (gradually or sudden) is diverse. To what extent these factors influence the development of IBH cannot be found in literature. This study showed no difference between affected horses and the control population of locally bred horses regarding the distribution of birth dates throughout the season.

It can be assumed that a longer allergen exposure of >7 months (born in April) makes no difference to a shorter allergen exposure of 2–3 months (born in August). This corresponds with the knowledge that at least during their first 6 months of life, foals do not develop an IgE response to allergens. The onset of the endogenous IgE production in foals was found to be delayed and occurred between 9 and 11 months of age depending on the individual [7]. Contrary to former assumptions [13], this can be seen as evidence that processes before the age of 6 months do not influence the occurrence of allergic reactions, at least not to that allergen which is relevant for IBH.

In this context, it is interesting that very young foals could not be vaccinated successfully in contrast to foals 6- and 9-months-old. Therefore, the immune system of foals younger than 6 months is not able to identify the extraneous vaccine and produce corresponding antibodies (Thein, personal communication, 2010). Contrary to this finding in the horse, the immune system of the bovine fetus seems to be able to detect the extraneous agent of bovine virus diarrhea as early as the second

Table 3

Age at import: comparison of prevalence of IBH in different age groups, Icelandic horses

Age Group Years	Prevalence of IBH in %	Age Group	Prevalence of IBH in %	P Value
≤February	6	1 up to ≥12	46	$P < .001$
≤February up to 1	7.5	2 up to ≤12	51	$P < .001$
≤February up to 2	8.1	3 up to ≥12	52	$P < .001$
≤February up to 3	10.5	4 up to ≥12	53	$P < .001$
≤February up to 4	11.9	5 up to ≥12	57	$P < .001$
≤February up to 5	15	6 up to ≥12	64	$P < .001$
≤February up to 6	19.5	7 up to ≥12	70	$P < .001$
1 up to 3	25.4	4 up to ≥12	53	$P < .001$
1 up to 4	25.9	5 up to ≥12	57	$P = .057053$
1 up to 5	29.7	6 up to ≥12	64	$P < .001$
1 up to 6	35.7	7 up to ≥12	70	$P < .001$

Table 4

Period between import and onset of IBH in relation to import age

Import Age Years	IBH-Onset After Import (Years)					
	1		2 bis 3		≥4	
	n	%	n	%	n	%
Up to 3	7	33	8	38	6	29
4–6	27	38	26	37	18	25
≥7	29	48	23	38	8	13

trimester of gestation and can become prenatally seropositive [19]. Calves produce antibodies within the first weeks of life [20]. There seems to be a varying period for the immune system of young animals concerning the ability to detect extraneous antigens, depending on the species.

In both groups of locally born horses, first diagnosis of IBH occurred most frequently at the age of 3 years. Within the first 5 years, 79% of the Icelandic horses and 61% of the animals of locally born breeds got IBH. These figures correspond well with the data found in literature [9,21]. In a previous study with Icelandic horses, 62% got IBH within the first 3 years [2]. Horses rarely develop IBH before the age of 12 months [21]. Commonly, the earliest symptoms can be detected at the end of their second summer beginning at the age of about 14 months. This finding, and the fact that the peak is reached at the age of 3, corresponds with the results of the study by Marti et al. [22], stating that foals start producing IgE at about the age of 6 months, and constantly higher levels of IgE can be found in the following 3 years. Among the animals older than 6 years, IBH was more prevalent in the other breeds (39%) than in the Icelandic horses (21%), as shown in Figure 1. This may be due to the fact that horses of other breeds are less frequently kept outside of closed stables and are therefore partly exposed to the allergen later in life than Icelandic horses.

Few studies examine the age at the time of import as a factor in development of IBH. Horses that were imported between the age of 6 months and 4 years showed a lower prevalence (28%), whereas horses imported between the age of 5 and 9 years had a higher prevalence (50% [9]). In another study, no correlation was found [5]. The data of the present study show that the risk of IBH increases with age at import.

Data on horses imported as foals in their first winter were remarkable. Weanlings imported at 3–7 months are 7–10-month-old when first exposed to the allergens and successfully develop immunological tolerance. With a prevalence of 6%, they are affected by IBH almost as much as locally born Icelandic horses with a declared prevalence of 1.5%–8.2% [2,16]. From these data, we concluded that immunological tolerance can develop partially at the end or exclusively at the end of the first year. Hence, the phase for shaping immunological tolerance in horses is longer than formerly supposed. The fact that horses imported at the age of 6 months, with a first possible allergen exposure at the age of 7 months have approximately the same low risk than locally born horses allows the conclusion that prenatal and early postnatal allergen exposure of the horse is fairly irrelevant.

Lasting immunological tolerance can also develop after the foal stage, although the data for this study show that chances to develop allergen tolerance decreases with age. According to this data, a 7-year-old imported horse has a 64% risk for IBH, whereas horses imported at age ≥ 12 years has a risk of 80%. The immune system seems to gradually lose its ability to adapt to new allergens.

Most horses caught IBH during their first year after import (42%), of which one-fourth contracted IBH within only a few months. In the second year after import, 30% got affected with IBH. In a study describing horses

imported to Germany [9], similar results are described. Data used for this study were mostly collected from riding horses, which were about 6 year old at import on average. As seen in the present study also, their mature immune system therefore reacts faster to allergen exposure than the immature immune system of locally born horses (Fig. 1, peak of outbreak 3 years after birth/allergen exposure).

Horses imported at an age of at least 7 years seem to be affected earlier after import than horses imported at younger age (shown in Table 4). Taking the small number of animals into account, this finding could be coincidental, but it correlates with the results stating a slower reaction of an immature immune system (of locally bred horses) as opposed to the fully developed immune system of (imported) adult horses [13]. Usually, horses were imported at an age of 5 years to 7 years.

5. Conclusion

The following can be summarized concerning the possible period for the development of immunological tolerance:

The duration of allergen exposure in the first 10 months of life has no influence.

For locally born foals, the risk of getting IBH is highest in their third year (3 years after first allergen contact).

For adult imported horses, the risk of getting IBH is highest in the first year after import (1 year after first allergen contact).

Horse's IgE-production which is relevant for the development of IBH does not start before the age of 6 months and increases during the next 3 years [22].

Prevalence of IBH for imported foals with first allergen exposure between 4 and 9 months is nearly the same as for locally born foals.

The finding supported from the data of this study may influence development and application of a therapy to induce immunological tolerance to prevent IBH.

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