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Predominant Right Leg Dysfunction Without Asymmetric Muscle Inflammation in CD1 Swiss Mice With Coxsackievirus B1-Induced Myositis

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JONGEN, P. J. H, P. ELING AND L. B. A. VAN DE PUTTE. *Predominant right leg dysfunction without asymmetric muscle inflammation in CD1 Swiss mice with Coxsackievirus B1-induced myositis.* PHYSIOL BEHAV **59**(4/5) 763–768, 1996.—To establish the existence of predominant right leg involvement in Coxsackievirus B1-induced myositis (CB1 myositis) 189 neonatal CD1 Swiss mice were inoculated with 300 pfu CB1, and regularly observed for posture, mobility, and gait. After 2 and 4 weeks, quantitative comparison of motor dysfunction of right and left leg yielded an asymmetry score; on light microscopy mononuclear cell infiltration and muscle fiber necrosis were quantified in bilateral hamstring muscles, using a five-grade scale (0–4). Motor asymmetries were seen during acute viral myositis as soon as hind leg dysfunction appeared, and animals with a predominant dysfunction of one leg preserved that preference throughout the observation period. At 2 weeks, mice with predominant right leg dysfunction ($n = 34$) significantly outnumbered those with predominant left leg dysfunction ($n = 11$) ($p = 0.01$). At 2 and 4 weeks, infiltration and necrosis in hamstrings from legs with predominant dysfunction were not higher than in those from contralateral legs, and infiltration in right-sided hamstrings was not higher than in left-sided ones, nor was infiltration at 4 weeks. At 4 weeks right-sided muscles were more necrotic (mean ± SD, 1.8 ± 1.5) than left-sided muscles (1.1 ± 1.2; $p = 0.03$). In the absence of predominant inflammatory disease of the right leg, we interpret the hind leg asymmetry as a preferential use of the left leg, due to left-leggedness, and suggest that in CD1 Swiss mice left-leggednes is associated with increased susceptibility to CB1 myositis.

Coxsackievirus B Myositis Murine Asymmetry Lateralization Pathology

INOCULATION of the Tucson strain of Coxsackievirus B1 (CB1) in neonatal CD1 Swiss mice causes, within 1 week after infection, an acute viral myositis of the hind leg musculature, histologically characterized by widespread necrosis of muscle fibers and diffuse infiltration of polymorphonuclear and mononuclear cells (22,27,32). Abnormalities in posture and gait appear a few days later (22,27,32). After 2 weeks the inflammation develops into a chronic phase, CB1-induced myositis (CB1 myositis), when virus can no longer be cultured from muscle tissue (27,32). CB1 myositis is thought to have an autoimmune origin and only occurs in the presence of T lymphocytes (35,36). For its clinical, electromyographic, and histological resemblance to human polymyositis (8), CB1 myositis is considered an experimental model for polymyositis (26,32). Like the preceding acute viral myositis, CB1 myositis principally involves the proximal hind leg muscles, and weakness shows itself as decreased mobility, abnormal posture, and a waddling gait (24,26,27,32). Severely affected animals develop a flexion deformity (27,32). In contrast to other murine models for polymyositis (23,26), the motor abnormalities in CB1 myositis have been reported to be asymmetric, suggesting the predominant involvement of one limb (24,27,32,35,36). Curiously, the right leg seemed more affected than the left one, both on observation and on qualitative microscopy (26,27,32,35). At present, however, no quantified observational data have been reported on predominant right leg dysfunction in CB1 myositis, nor has its morphological basis been established on quantitative

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microscopy (24,26,27,32,35,36); no plausible explanation has been put forward for the right leg bias. To answer these questions, we quantified motor asymmetries in mice with CB1 myositis on repeated observation and studied mononuclear cell infiltration and muscle fiber necrosis in right- and left-sided hamstring muscles on quantitative microscopy.

METHOD

Virus and Cells

The CB1 Tucson strain was a gift from L. Minnich, M.S., and Dr. C. George Ray, University of Arizona (Tucson, AZ) (24,27). Buffalo green monkey kidney cells (BGM cells) were used for growth of CB1 virus stocks and for plaque assays. BGM cells were grown in Eagle's Minimum Essential Medium with Earle's salts, 10% fetal bovine serum (FBS), penicillin (100,000 U/l), and gentamicin (50 mg/l). Maintenance medium contained 3% FBS. Virus was stored at −70°C. Dilutions of virus used in vivo were made in phosphate-buffered saline (PBS).

Animals and Experimental Design

Specific pathogen-free random-bred pregnant CD1 Swiss mice were purchased from Charles River Wiga GmbH (Sulzfeld, Germany) and allowed to deliver. Offspring were randomly selected, inoculated, and caged with maternal mice in groups of 10–14 animals. A total number of 189 mice were inoculated IP within 24 h after birth with 300 pfu of CB1 in 0.1 ml PBS (18–20,27). Twenty-two control animals were injected with 0.1 ml PBS.

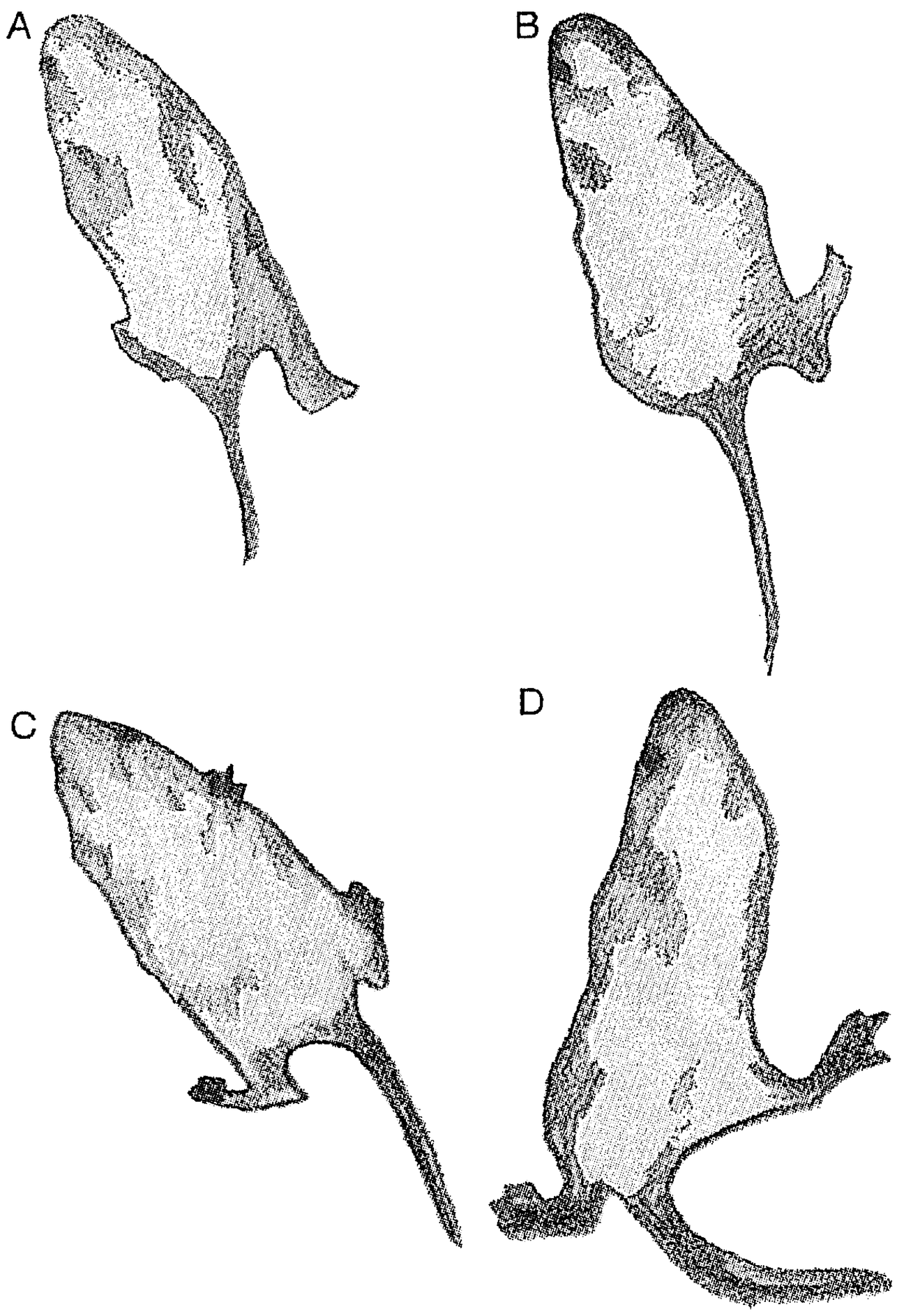

FIG. 1. (A–D) Normal and abnormal gait patterns in CD1 Swiss mice 4 weeks after CB1 inoculation, observed from above. (A) Normal hind leg function: right leg stretched with fully extended hip joint and semiextended knee joint, left leg practically invisible due to fully flexed hip and knee joints. (B) Right leg dysfunction (score R): right hip joint partially extended and abducted, knee joint semiflexed. (C) Less right leg dysfunction than left leg dysfunction (score R < L): right leg partially visible due to incomplete hip ands knee flexion. (D) More severely affected mouse than in (C), with other direction but the same degree of leg asymmetry, R > L. For detailed description of scores see the Method section.

Animals were housed under normal laboratory conditions of 22 ± 1°C on a standard light:dark schedule (12:12; lights on: 0800–2000 h) and with free access to standard laboratory diet and water.

Observation of Hind Leg Function

To better recognize abnormal movements and motor patterns, we first performed a pilot study with other mice, making videos for detailed visual analysis. After inoculation mice were coded and observed every day during the first 2 weeks, thereafter every other day until 4 weeks after inoculation. One experimenter (PJ) did all observations. For observation a single mouse was placed in the middle of a open square box measuring 25 cm width, 50 cm length, and 20 cm height, the bottom of which was covered by a sheet of paper with a slightly rough surface to provide sufficient grip. The paper was changed regularly to avoid distraction by odors from other mice.

After a short period of adaptation to the experimental condition, most animals appeared to moved freely inside the box. Mice that were indolent or immobile were stimulated mechanically by gently pulling at the base of the tail, to a maximum of three times. Observations were made during the light period with a room temperature of 22 ± 1°C and at the same time of day. To detect consistent hind leg asymmetries, each animal was observed during 60 s for posture, spontaneous mobility, pattern of gait (waddling, dragging of a limb, flexion deformity), speed of gait, and ability to climb against the wall of the box. Having thus obtained an overall assessment of right leg dysfunction and left leg dysfunction, quantitative comparison of the two yielded a score for the asymmetry of hind leg dysfunction (hind leg asymmetry) as follows: R, right leg dysfunction and normal left leg function; R >> L, much more right leg dysfunction than left leg dysfunction, with right leg not or hardly contributing to locomotion; R > L, more right leg dysfunction than left leg dysfunction, with both legs contributing to locomotion; R = L, no difference between right leg dysfunction and left leg dysfunction; R < L, less right leg dysfunction than left leg dysfunction, with both legs contributing to locomotion; R << L, much less right leg dysfunction than left leg dysfunction, with left leg not or hardly contributing to locomotion; L, left leg dysfunction and normal right leg function (for illustration see Fig. 1). Scoring was blinded for the results of the preceding observations. It appeared that in the majority of mice at least two of the scores of days 13, 14, and 15 were identical, and that score was considered the week 2 score. In the other cases we also took into account the scores of days 11 and 12, and the score that occurred most frequently was considered the week 2 score. The same procedure was applied to obtain the week 4 score (days 24, 26, and 28, and days 20 and 22, respectively). Thus, at 2 and 4 weeks animals with dysfunction of one or two hind legs were classified according to direction and degree of hind leg asymmetry.

Histological Examination

At 2 weeks after inoculation every second animal ($n = 31$) was killed by cervical dislocation under ether anesthesia for histological examinations. The remaining animals ($n = 33$) were killed at 4 weeks for the same examinations.

Immediately after killing, quadriceps, hamstring, and gluteus muscles were removed in toto and placed in buffered formalin. Muscles were paraffin-embedded and sectioned at 6 μm. In a previous study we found that most extensive inflammatory and myopathic changes occurred in hamstring muscles, in agreement with previous reports (19,38) and with the fact that these muscles were the most atrophic on macroscopy (27,32). We also demonstrated that the histological changes (mononuclear cell infiltration, muscle fiber necrosis, central nuclei, fiber atrophy) were evenly distributed over the whole length of a muscle (20), and that cross section areas of hamstring muscles at 2 weeks did not differ significantly from those at 4 weeks (19). Therefore, mid-portion transverse sections of left and right hamstring muscles were stained with haematoxyline-phloxine-saffron and examined light microscopically (magnification 250 ×). Slides were coded. To assess muscle fiber damage (the morphological basis of hind leg dysfunction), and cellular inflammation (its underlying cause), we quantitated mononuclear cell infiltration and muscle fiber necrosis per section using a five-grade scale, as described previously (18–20). Infiltrating mononuclear cells per section: absent (0), less than 10 (+1), 10–50 (+2), 50–100 (+3), more than 100 (+4); necrotic fibers per section: absent (0), 1–5 (+1), 5–15 (+2), 15–25 (+3), more than 25 (+4).

Statistics

In mice with asymmetric leg dysfunction the McNemar (sign) test for discordant pairs was used to compare the number of mice with predominant dysfunction of the right leg (R > L, R >> L, or R) to the number of mice with predominant dysfunction of the left leg (R < L, R << L, or L). Degrees of cell infiltration and fiber necrosis are given as mean values ± SD. The Wilcoxon test for matched pairs was used to compare values from right-sided muscles to those from left-sided muscles, and to compare values from legs with predominant dysfunction to those from contralateral legs. In all tests a value of $p \leq 0.05$ was considered significant.

RESULTS

Observational Data

From 189 CB1 inoculated mice 46 died in the first week after infection from generalized viral disease, and five more in the second week, yielding a 2-week mortality of 27%. Of the surviving 138 mice, 64 (46%) had a dysfunction of one or both hind legs at 2 weeks. Commonly, hind leg dysfunction became detectable late in the first untill early in the second week. Asymmetries were seen as soon as leg dysfunction became manifest, and they were consistent in that, as soon as animals had a predominant dysfunction of one leg, they preserved that preference throughout the observation period. In none of the control mice were motor asymmetries observed nor in the fore legs of the CB1-inoculated animals.

Figure 2 shows the frequencies of scores for hind leg asymmetry at 2 weeks. The number of animals with a predominance of right leg dysfunction (R, R >> L, R > L) ($n = 34$; 53%) was significantly higher than the number of animals with predominance of left leg dysfunction (R < L, R << L, L) ($n = 11$; 17%) ($p = 0.01$). Nineteen mice had a symmetric dysfunction (30%). Thirty-one mice were followed for 4 weeks. In the additional 2 weeks no animal died. In some mice leg function improved, in eight animals leading to a decrease of asymmetry, without affecting the direction of asymmetry.

Histological Data

Degrees of mononuclear cell infiltration and muscle fiber necrosis in hamstrings from legs with predominant dysfunction did not differ from those in hamstrings from contralateral legs, both at 2 weeks and at 4 weeks (Table 1). Moreover, degree of cell infiltration in right-sided muscles did not differ from that in the left-sided muscles at 2 and 4 weeks, nor the degree of

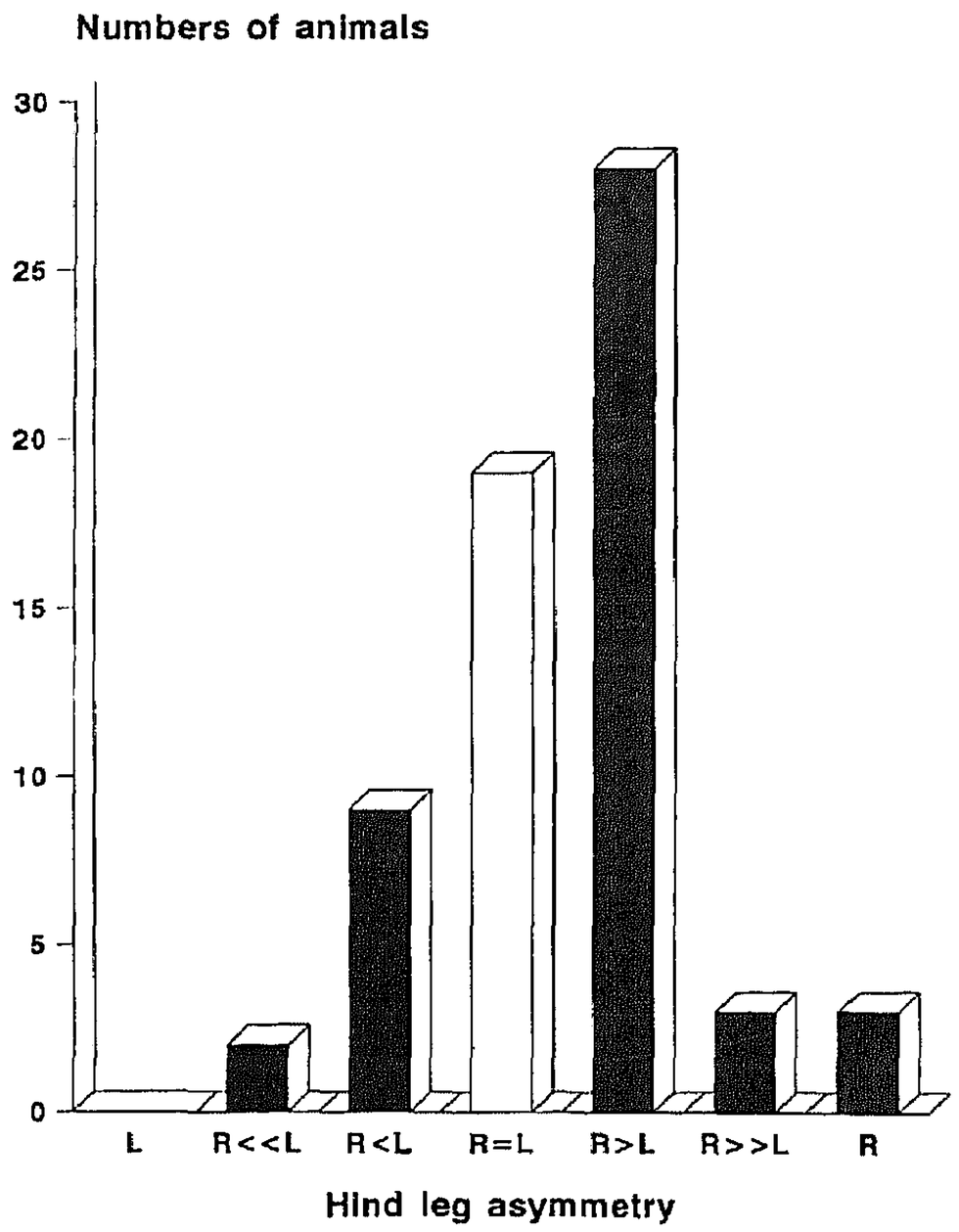

FIG. 2. Scores for hind leg asymmetry [i.e., right leg dysfunction (R) compared to left leg dysfunction (L)] in 64 CD1 Swiss mice 2 weeks after CB1 inoculation. See the Method section for details.

necrosis at 2 weeks. At 4 weeks right-sided muscles were more necrotic than left-sided ones.

DISCUSSION

In quantitative observations of motor asymmetries in CD1 Swiss mice with CB1 myositis we clearly established a preferential dysfunction of the right hind limb: at 2 weeks 53% of affected animals had a predominant dysfunction of the right leg, being 76% of the animals with asymmetric leg dysfunction. In contrast, we obtained no evidence for a predominant right leg involvement, because inflammation in right-sided hamstrings was not higher than in left-sided ones, nor were inflammation and necrosis in legs with predominant dysfunction higher than in contralateral legs. Although it cannot be excluded that to a certain degree asymmetric muscle involvement may play a role in some mice, our histopathological data as a whole fail to explain the evident right-bias in leg dysfunction. Remarkably, motor asymmetries occurred as soon as leg dysfunction became observable, and in an individual animal the direction of asymmetry was preserved throughout the observation period. Because CB1 myositis develops from 2 weeks on (32,35), the asymmetry has to relate to the phase of acute myositis, and because there were no histopathological asymmetries, the motor asymmeties cannot result from the myositis as such.

Via the IP route inocula may inadvertently be deposited in various intra- and extraperitoneal organs. Thus, CB1 inoculation might lead to damage of retroperitoneal neural structures, and to neurogenic muscle weakness. If so, the handedness of technicians could theoretically predispose to right- or left-sided neural damage. However, it is highly unlikely that retroperitoneal deposition occurs in as many animals as we found having predominant right leg dysfunction. Moreover, histological examination of the peripheral nervous system by various investigators were normal (24,27,32), and gluteus, hamstring, and quadriceps muscles showed no neurogenic changes (19,27,32). Another explanation for the predominant right leg dysfunction might be that in the acute phase of generalized viral disease cerebral hemispheres become slightly inflamed, as has been reported in Coxsackievirus B viral myositis (22,24), and that predominant right leg dysfunction results from a left-sided encephalitis. However, observation gave no signs of spasticity, nor gait disturbances suggestive of a cerebral lesion. In addition, on light microscopy of cerebral hemispheres no abnormalities were found, neither by us (data not shown) nor by others (27,32). Therefore, we think there is a third and more likely explanation. As yet the predominant right leg dysfunction has been interpreted as that the right leg functions less than the left one (24,27,32,35). However, our findings justify the alternative view that affected mice preferentially use their left legs, due to left-leggedness.

Postural and behavioral asymmetries have been documented extensively in mice and rats (10,16,30,37), even in their first days of life (1,10). In experimental conditions mice show a pronounced, enduring, and not task specific preference for the use of either the right or the left forepaw (7,31). Most murine strains have a right paw preference, but some preferentially use the left paw (21). Interestingly, the degree of lateralization increases under stress conditions and after practice (2,28), especially practice in the postnatal phase (1), and once obtained lateralization remains present throughout the animal's life span (1). As to CB1 myositis, in neonatally inoculated mice acute and chronic disease means a stressful condition and bilateral muscle weakness forces the animal to practice in the postnatal days; hence, hind leg lateralization may increase considerably and become manifest. The circumstance that adult mice have less potential for increase of lateralization can explain why predominant right or left leg dysfunction has not been reported in other animal models for myositis, using adult mice (23,26).

The fact that at 4 weeks right-sided hamstring muscles were more necrotic than left-sided ones does not contradict our view, because it has recently been demonstrated in humans that exercise during the active phase of polymyositis improves muscle strength (11,17). Likewise, due to their spontaneous mobility, mice forcedly train their leg muscles and might induce regenera-

TABLE 1

DEGREES (MEAN ± SD) OF MONONUCLEAR CELL INFILTRATION AND MUSCLE FIBER NECROSIS IN CD1 SWISS MICE WITH CB1 MYOSITIS AT 2 WEEKS AND 4 WEEKS AFTER INOCULATION

	2 Weeks ($n = 31$)	4 Weeks ($n = 33$)
Mononuclear cell infiltration		
Right side	3.3 ± 1.2	1.8 ± 1.3
Left side	3.7 ± 0.7	1.5 ± 1.3
Predominant side	3.9 ± 0.8	2.1 ± 1.2
Contralateral side	3.6 ± 1.2	2.0 ± 1.0
Muscle fiber necrosis		
Right side	2.6 ± 1.5	1.8 ± 1.5*
Left side	2.9 ± 1.4	1.1 ± 1.2
Predominant side	3.2 ± 1.1	2.5 ± 1.3
Contralateral side	2.4 ± 1.4	2.3 ± 1.7

Cross sections of right and left hamstring muscles, and of muscles from legs with predominant dysfunction (predominant side) and contralateral legs.

* $p = 0.03$, Wilcoxon test for matched pairs.

tion. In consequence of their lesser use, right-sided muscles will undergo less training-induced regeneration and show relatively more necrosis.

In asymmetrically affected CD1 Swiss mice the percentage of left-lateralized animals (76%) is higher than the percentage of left-lateralized animals in strains with documented left lateralization (e.g., the ICR strain, 68%) (10,21,30,37). In view of the fact that the direction of an individual mouse's side preference is genetically determined (1,9,15), we suggest a specific relationship to exist in individual CD1 mice between left-leggedness on the one hand, and susceptibility to CB1 viral myositis and CB1 myositis on the other. In line with the Geschwind–Galaburda hypothesis on the association between anomalous cerebral dominance and immune disorders (14), consistent relations were found between left-handedness and autoimmune disorders. Patients with allergies, asthma, or colitis ulcerosa have a higher incidence of left-handedness than controls, and colitis ulcerosa and thyreoiditis are consistently more common in left-handers than in right-handers (4). Likewise, left-handed persons have an increased percentage of suppressor–inducer T cells (34), nonright-handers show an elevated incidence of circulating autoantibodies (5), and nonright-sided individuals have a significantly lower interleukin-2 (IL-2) production (6). Results in animals studies parallel those in humans (9,12,25). Left-pawed C3HeNCrMTV mice have a lower natural killer (NK) cell activity and mixed leukocyte reaction (MLR) than their right-pawed strain mates, and in the balb/cJ strain, left-pawed mice have lower cytotoxic T-lymphocyte response (CTL) and MLR than right-pawed animals (12). Importantly, NK cell activity and CTL are major defence mechanisms against viral disease (3,12,22), and for an adequate antiviral antibody response the positive effect of IL-2 on the proliferation of activated T cells is essential (29). Mice with CB1 myositis have a prolonged presence of viral RNA in affected muscles (4 weeks), which is thought to play a role in the development to CB1 myositis (33,34). Obviously, the delayed clearance of viral RNA indicates that antiviral immune mechanisms operate inadequately (32,35,36). Therefore, a defective CTL may play a role in secondary autoimmune reactions (3). From this we hypothesize that left-legged CD1 Swiss mice—in contrast to their right-legged strain mates—have a genetically determined impairement of immune function, predisposing them to develop CB1 myositis. Affected CD1 mice may also have a genetically determined high degree of lateralization, because it is known that a high degree of lateralization is associated with decreased immune responsiveness: in mice selectively bred for either strong or weak degree of lateralization, only mice with a high degree of lateralization had lower immune functions than controls, manifest as reduced MLR, CTL, NK cell activity (13). Finally, the association between immune function and paw preference is a strain-dependent phenomenon (12). In this respect, we mention that, from various strains tested, only left paw balb/c mice had lower NK and MLR (12), and that balb/c mice are also the only other strain in which CB1 myositis can be induced, be it to a limited degree (22,27).

To conclude, we demonstrated that CD1 Swiss mice with CB1 myositis have a predominant dysfunction of the right leg, and that, contrary to expectation, right-sided muscles are not more inflamed than left-sided ones. We intrepret the observed asymmetry as a preferential use of the left leg (i.e., as a manifestation of left-leggedness), and suggest that in CD1 Swiss mice left-leggednes is associated with impaired immune functions, rendering them susceptible to CB1 myositis.

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