ORIGINAL ARTICLE

Maternal infanticide and low maternal ability in cerebellar mutants *Lurcher*

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Abstract

OBJECTIVE: One of the common, but less studied deficiencies in mouse models of cerebellar disorders is impaired breeding capacity. Nevertheless, there is no extensive study in *Lurcher* (Grid2^{Lc}) mice, a model of olivocerebellar degeneration. The aim of this work was to analyze a breeding capacity of these mutants.
METHODS: *Lurcher* females mated with healthy wild type males were compared with two control groups: wild type females mated with wild type males and wild type females mated with *Lurcher* males. The breeding capacity of *Lurcher* mice was analyzed using a fertility rate, mating capability and pups survival rate through three consecutive litters.
RESULTS: *Lurcher* dams did not show significantly reduced fertility and mating capability. Nevertheless, their breeding capacity was affected by reduced litter size, maternal infanticide and higher pup mortality during the maternal care period.
CONCLUSION: *Lurcher* mice are fertile and mating capable cerebellar mutants, but their breeding capacity is reduced due to the postpartum behavioral abnormalities. With regard to hyper-reactivity of the hypothalamo-pituitary-adrenal axis followed by behavioral disinhibition during stressful events in *Lurcher* mutants, we hypothesize that the lower breeding capacity is associated with these endocrine and behavioral abnormalities.

Abbreviations:

Agtpbp1^{pcd}	- purkinje cell degeneration mutation
BC_a	- bias corrected and accelerated method
CMH	- Cochran-Mantel-Haenszel test
GluRδ2	- δ2 glutamate receptor
Grid2^{Lc}	- *Lurcher* mutation
HPA	- hypothalamic-pituitary-adrenal axis
Lc$^{(wt)}$	- *Lurcher* females mated with wild type males
nr	- *nervous* mutation
PP1	- postpartum day 1
PP2	- postpartum day 2
PP30	- postpartum day 30
Reln^{rl}	- *reeler* mutation
Rora^{sg}	- *staggerer* mutation
SEM	- standard error of the mean
wt$^{(Lc)}$	- wild type females mated with *Lurcher* males
wt$^{(wt)}$	- wild type females mated with wild type males

INTRODUCTION

Cerebellar disorders are associated with ataxia, dysarthria and difficulty with eye movements. Structural and/or functional cerebellar abnormalities also affect cognition, regulation of emotion and social interaction processing (Schmahmann 2004). A less expected, but common deficiency in mouse models of cerebellar disorders is impaired reproductive performance and offspring productivity. Aberrations in the vaginal estrous cycle and ovarian abnormalities have been found in *staggerer* (*Rora*^{sg}) mice (Guastavino *et al.* 2005; Guastavino & Larsson 1992). Reduced reproductive performance has also been found in *reeler* (*Reln*^{rl}) and *nervous* (*nr*) mutants (Guastavino *et al.* 1993; Sidman & Green 1970). Smaller litter size and difficulties with pup care have been described in Purkinje cell degeneration (*pcd*; *Agtpbp1*^{pcd}) mice (Mullen *et al.* 1976). It has been assumed that affected motor coordination in cerebellar mutants influences sexual activity, nest-building behavior and pup rearing (Chen *et al.* 2007; Guastavino *et al.* 1993), but other authors have suggested that this behavioral deficiency could be caused by a global effect of the mutation on other systems (e.g. endocrine system) (Bulloch *et al.* 1982).

Although mating success, reproductive performance and maternal ability in cerebellar mutant mice have occasionally been studied for a long time, none of these studies focused on *Lurcher* mice. *Lurcher* (*Grid2*$^{Lc/+}$) mutants constitute a natural model of hereditary olivocerebellar degeneration (Phillips 1960). The degenerative process is caused by a mutation of the δ2 glutamate receptor (*GluRδ2*) gene (Zuo *et al.* 1997). GluRδ2 is predominantly expressed by cerebellar Purkinje cells and, at lower levels, in some hindbrain neurons (Araki *et al.* 1993). Constitutive activation of *GluRδ2*^{Lc} causes an inward current and consequent excitotoxic death of Purkinje cells (Norman *et al.* 1995); this is followed by the death of granule, basket and stellate cells and inferior olive neurons due to the disappearance of connective pathways (Caddy & Biscoe 1979; Heckroth & Eisenman 1991; Zanjani *et al.* 2006). The mutant mice are semi-dominant heterozygous. Homozygous individuals (*Grid2*$^{Lc/Lc}$) die shortly after birth due to massive loss of mid- and hindbrain neurons (Cheng & Heintz 1997). *Lurcher* mice are characterized by the cerebellar ataxia (Hilber & Caston 2001), cognitive deficits (Hilber *et al.* 1998), behavioral disinhibition (Hilber *et al.* 2004) and hyper-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Frederic *et al.* 1997).

Lurcher mutants are fertile, although the litter size of *Lurcher* females is reduced (Phillips 1960); however, the breeding capacity of *Lurcher* females has not been extensively studied yet. In view of this fact, our objective was to test the reproductive performance and maternal ability of *Lurcher* dams over the course of three consecutive litters and to compare them with their healthy littermate controls.

MATERIALS AND METHODS

Animals

Lurcher (Lc) mutants and their healthy wild type (wt) littermates (B6CBA strain) were used. Females were housed separately in plastic cages (20 x 25 cm) with wooden shavings in a temperature and humidity controlled room with a standard 12/12 hours light/dark cycle. Standard commercial pellet diet and water were available *ad libitum*. The experiment was performed in compliance with EU Guidelines for scientific experimentation on animals and with permission of the Ethics Committee of the Faculty of Medicine in Pilsen, CZ.

Reproductive performance, maternal ability and breeding capacity assessment

Three experimental groups of female mice were used. *Lurcher* females were mated with wild type males (Lc$^{(wt)}$, *n=13*). Two control groups consisted of wild type females mated with wild type males (wt$^{(wt)}$, *n=13*) and wild type females mated with *Lurcher* males (wt$^{(Lc)}$, *n=13*). Dams from Lc$^{(wt)}$ and wt$^{(Lc)}$ groups should have theoretically breed in Mendelian ratios, i.e. 50% *Lurcher* and 50% of wild type pups. Therefore, the wt$^{(Lc)}$ group served as an ideal control for both litter size and pup viability assessment. *Lurcher* and control females were followed through three reproduction cycles. Females were mated for the first time at the age of 2 months. Each reproduction cycle consisted of a maximum of 3 weeks of mating (the male was removed when the female became obviously pregnant, or at the end of the 3 week mating period), the residual period of gravidity (i.e. delivery would theoretically occur 0–3 weeks after the male was removed), 4 weeks of pup-rearing and 2 weeks of rest time after the pups were weaned.

The reproductive performance was evaluated using the fertility rate, mean delivery day and litter size on the second postpartum day (PP2). The fertility rate was the percentage of mated females giving birth to pups (born dead or alive). The delivery day was calculated as the sum of the mating time and the residual period of gravidity and served as an indicator of the mating time necessary for conception (assuming that the pregnancy duration was constant). Mean litter size on PP2 was calculated only for dams with at least 1 live pup at that time point. To avoid stressing the mothers, especially *Lurcher* dams, pups were not counted immediately after parturition; instead they were counted on PP2.

Maternal ability was evaluated as maternal infanticide rate and pup survival rate. The maternal infanticide rate was calculated as the percentage of dams giving birth to pups which cannibalized their complete litter on PP1. Since the pups were counted on PP2, cannibalizing only individual pups on PP1 was undetectable. Pups survival rate was calculated as the percentage of pups surviving from PP2 until weaning on PP30. To lessen the emotional hyper-reactivity of *Lurcher* mutants during stressful situations, dams were

Tab. 1. Fertility rate and mean delivery day (± SEM) of *Lurcher* and wild type control dams in individual litters.

	Fertility rate [%]				Delivery day			
	$Lc^{(wt)}$	$wt^{(Lc)}$	$wt^{(wt)}$	*p-value* [a]	$Lc^{(wt)}$	$wt^{(Lc)}$	$wt^{(wt)}$	*p-value* [b]
1st litter	83.33	83.33	92.31	0.717	28.82 (±2.78)	24.42 (±1.70)	24.08 (±0.87)	0.349
2nd litter	72.73	80.00	100.00	0.129	26.29 (±2.77)	23.22 (±1.33)	24.08 (±1.73)	0.445
3rd litter	70.00	70.00	83.33	0.679	21.71 (±0.42)	26.86 (±3.09)	27.90 (±2.54)	0.315

Note: Fertility rate = total number of females giving birth to pups (born dead or alive)/total number of mated females ×100; Delivery day = number of days after start of mating to delivery; $Lc^{(wt)}$ = *Lurcher* female mated with wild type male; $wt^{(Lc)}$ = wild type female mated with *Lurcher* male; $wt^{(wt)}$ = wild type female mated with wild type male
[a] Freeman-Halton extension of Fisher's exact test; [b] Kruskal-Wallis ANOVA.

not separated (e.g. pup weighing, nest-building behavior scoring) from their pups to avoid modifying natural maternal behavior.

Breeding capacity was the number of live pups at weaning time (PP30). All mated females were involved in the assessment of this parameter. The number represents the number of pups produced in one litter per one female of the group and it is the final measure of both reproductive performance and maternal care ability.

Statistical analysis

The comparison of *Lurchers* ($Lc^{(wt)}$) fertility rate and maternal infanticide rate for three consecutive litters with each control group of wild type dams ($wt^{(wt)}$, $wt^{(Lc)}$) was performed using the Cochran-Mantel-Haenszel (CMH) test for $2 \times 2 \times K$ contingency tables. CMH statistics allows for the analysis of three nominal variables ($2 \times 2 \times K$), where two variables are independent (groups) and the third variable identifies the repeats (litters). The homogeneity of odds ratios, assumptions for the CMH test, was verified using the Breslow-Day test. The analysis of each litter was done separately using the Freeman-Halton extension of Fisher's exact test for 2×3 tables and Fisher's exact test for post-hoc analyses to find any differences between two groups. The mean delivery day, pup survival rate and mean litter size were evaluated using the Kruskal-Wallis ANOVA. Multiple comparisons were performed using the bootstrapping 95% confidence intervals (95% CI) for the difference in the means and two-sample permutation test. The 95% CI for the difference in means was estimated using the bias corrected and accelerated (BC_a) method. The BC_a method can be applied to the construction of nonparametric confidence intervals. The two-sample permutation test requires few assumptions (e.g. normal distribution) and thus can be used for post hoc analysis with Kruskal-Wallis ANOVA. Both resampling procedures were based on 10,000 replicates. Violation of Gaussian distribution assumption was verified using the Shapiro-Wilk test. Differences were considered statistically significant if $p<0.05$. Statistical analyses were performed using R 2.14.0 (GNU) for Mac OS X. Quantitative data are presented as mean ± standard error of the mean (SEM).

RESULTS

Results of the reproductive performance assessment are presented in Table 1. *Lurcher* dams did not show any significant changes in fertility rate (CMH test: $Lc^{(wt)}$ vs. $wt^{(wt)}$: $\chi^2=2.46$, $p=0.117$; $Lc^{(wt)}$ vs. $wt^{(Lc)}$: $\chi^2=0.05$, $p=0.825$). Mutant fertility rates were not been significantly changed over three consecutive litters compared to both control groups (see Table 1). *Lurcher* dams also did not show significantly increased delivery day compared to control dams (see Table 1).

Although, mutant dams had no problems with mating and pregnancy, the CMH test showed a higher maternal infanticide incidence in *Lurchers,* within all three litters ($Lc^{(wt)}$ vs. $wt^{(wt)}$: $\chi^2=7.62$, $p=0.006$; $Lc^{(wt)}$ vs. $wt^{(Lc)}$: $\chi^2=12.10$, $p=0.001$), with the most prominent incidence in the 1st litter (see Table 2). Maternal infanticide was observed on PP1, and probably occurred immediately after parturition. Although the cause of pup death on PP1 could not be specified, pieces of carcass were not found; therefore the missing pups were assumed to be cannibalized. Since almost all litters of *Lurcher* females, during the first reproduction cycle, were cannibalized, pup survival rate as well as mean litter size on PP2 and PP30 could not be evaluated for the first litter. Consequently both of these parameters

Tab. 2. Maternal infanticide rate of *Lurcher* and wild type control dams in individual litters. Data are presented as a mean (± SEM).

	Maternal infanticide rate [%]			
	$Lc^{(wt)}$	$wt^{(Lc)}$	$wt^{(wt)}$	*p-value* [a]
1st litter	80.00	0.00	8.33	**<0.001** *
2nd litter	25.00	0.00	7.69	0.431
3rd litter	42.86	14.29	30.00	0.393

Note: Maternal cannibalism rate = total number of maternal cannibalism incidence/total number of parturitions × 100; $Lc^{(wt)}$ = *Lurcher* female mated with wild type male; $wt^{(Lc)}$ = wild type female mated with *Lurcher* male; $wt^{(wt)}$ = wild type female mated with wild type male
[a] Freeman-Halton extension of Fisher's exact test
* $Lc^{(wt)}$ vs. $wt^{(Lc)}$: $p<0.001$; $Lc^{(wt)}$ vs. $wt^{(wt)}$: $p=0.002$; $wt^{(wt)}$ vs. $wt^{(Lc)}$: $p=1.000$ (Fisher's exact post-hoc test).

were analyzed for all three litters together. The results from the mean litter size and pup survival rate are presented in Table 3. *Lurcher* dams showed significantly lower litter size on PP2 and PP30 as well as a lower pup survival rate compared to both groups of wild type controls. Breeding capacity of $wt^{(Lc)}$ and $wt^{(wt)}$ control groups was similar since no significant differences in: (1) fertility rate (CMH test: $wt^{(wt)}$ vs. $wt^{(Lc)}$: $\chi^2=1.70$, $p=0.192$; see Table 1), (2) delivery day (see Table 1), (3) maternal infanticide (CMH test: $wt^{(wt)}$ vs. $wt^{(Lc)}$: $\chi^2=0.76$, $p=0.384$; see Table 2) or (4) pups survival rate and litter size on PP2 and PP30 (see Table 3) were found.

DISCUSSION

Reproductive performance, maternal ability and overall breeding capacity of *Lurcher* females were studied. Although, *Lurcher* dams did not show any changes in reproductive performance compared to both control groups, maternal ability to progress pups from delivery to weaning was significantly affected. This behavioral disruption led to an overall decrease in breeding capacity of mutants.

Lurcher females did not show significantly altered fertility rate or delivery day. The reproductive system, namely conception capability and course of pregnancy in *Lurcher* females, does not seem to be markedly affected by the mutation. Mutation related motor disturbances present in *Lurchers* probably do not interfere with mating and sexual activity. Furthermore, the absence of differences between wild type females mated with wild type males and those mated with *Lurchers* suggest normal fertility and sexual activity in *Lurcher* males. These results are in contrast with previous findings for other cerebellar mutants, where mating impairment was likely, at least in part, a consequence of gait abnormalities, problems with body balance and reduced male fertility (Guastavino 1982; Guastavino *et al.* 1993). The only impairment of reproductive performance in *Lurcher* females was smaller litter size on PP2. The present study was not focused on prenatal examination of the number of fertilized oocytes or number of embryos. Therefore it is difficult to associate the reduced litter size, shortly after birth, as being prenatal related or perinatal related, i.e. natural pup death or maternal cannibalism.

Increased maternal infanticide, especially in primiparous dams and lower pup survival rate indicated poor maternal ability in *Lurcher* mutants. With regard to previously published results for other cerebellar mutants (Boufares *et al.* 1993; Bulloch *et al.* 1982) and unpublished observations, it was not assumed that maternal ability impairment was due to motor disorder in *Lurcher* dams. More likely it is indicative of a deficit in sensorimotor integration and affected emotionality of *Lurcher* mutants (Hilber *et al.* 2004; Porras-Garcia *et al.* 2005).

The cerebellar cortex can exert tonic inhibition on the amygdala, hippocampus and septum relative to the Papez circuit (Snider & Maiti 1976). Disruption of this suppression, by the mutant-related disappearance of Purkinje cells in *Lurcher* mutants, can induce changes in emotional behavior followed by an inability to select information during stressful events and the consequent loss of dependence on the environmental context.

Although, *Lurcher* mice have normal basal levels of adrenocorticotropic hormone (ACTH) and corticosterone (CORT), both hormones are dramatically elevated during mild stressful situations including common daily low stress events (Frederic *et al.* 1997), e.g. home-cage cleaning, handling or transfer to laboratory. Increased levels of corticotropin-releasing hormone (CRH), followed by increased CORT secretion, in cerebellar mutants (Frederic *et al.* 1997; Frederic *et al.* 2006), can influence the function of the amygdala and hippocampus, which are sensitive to both of these hormones (Giesbrecht *et al.* 2010; Maras & Baram 2012; Kavushansky & Richter-Levin 2006). The amygdala as well as hippocampus are also involved in the sensorimotor gating system (Miller *et al.* 2010), and play a role in stress and anxiety-related behavior. Therefore, affection of the central inhibitory system, together with the HPA axis hyper-reactivity, in *Lurcher* mutants can trigger a disproportionate behavioral reaction (Lorivel *et al.* 2010) and abnormal maternal behavior, e.g., neglecting, eating or killing their own pups. This hypothesis is supported by Poley (1974) who described higher stress reactivity to environmental stimuli as a factor causing maternal infanticide or cannibalism in rodents. The effect of CORT could be potentiated by the physiological increase in CORT level after the parturition (Zarrow *et al.* 1972) which has been suggested to modulate ongoing maternal behavior (Rees *et al.* 2004).

Tab. 3. Litter size and pup survival rate of *Lurcher* and wild type control dams. Data are presented as mean (± SEM).

	Litter size PP2	Litter size PP30	Pup survival rate
$Lc^{(wt)}$	3.92 (±0.47)	1.78 (±0.72)	49.21 (±17.84)
$wt^{(Lc)}$	6.65 (±0.31)	6.15 (±0.35)	91.86 (±3.59)
$wt^{(wt)}$	5.81 (±0.61)	5.61 (±0.60)	95.37 (±2.89)
p-value [a]	**0.008** [*]	**0.002** [†]	**0.015** [‡]

Note: Pup survival rate = number of weaned pups/number of live pups at PP2 × 100; PP2 = post-partum day 2; PP30 = post-partum day 30 (the weaning time); $Lc^{(wt)}$ = *Lurcher* female mated with wild type male; $wt^{(Lc)}$ = wild type female mated with *Lurcher* male; $wt^{(wt)}$ = wild type female mated with wild type male

[a] Kruskal-Wallis ANOVA with difference of means (95% CI for difference) and two-sample permutation test as a post-hoc analysis

[*] $Lc^{(wt)}$ vs. $wt^{(Lc)}$: –2.74 (–3.96, –1.72), $p<0.001$; $Lc^{(wt)}$ vs. $wt^{(wt)}$: –1.89 (–0.49, –2.15), $p=0.028$; $wt^{(wt)}$ vs. $wt^{(Lc)}$: 0.85 (–0.44, 2.22), $p=0.229$

[†] $Lc^{(wt)}$ vs. $wt^{(Lc)}$: –4.38 (–5.84, –2.65), $p<0.001$; $Lc^{(wt)}$ vs. $wt^{(wt)}$: –3.83 (–5.66, –1.89), $p<0.001$; $wt^{(wt)}$ vs. $wt^{(Lc)}$: 0.54 (–0.82, 1.84), $p=0.433$

[‡] $Lc^{(wt)}$ vs. $wt^{(Lc)}$: –42.65 (–79.17, –5.56), $p=0.001$; $Lc^{(wt)}$ vs. $wt^{(wt)}$: –46.16 (–82.32, –10.33), $p<0.001$; $wt^{(wt)}$ vs. $wt^{(Lc)}$: –3.52 (–12.02, 5.61), $p=0.806$.

Finally, the altered litter size on PP2 could be also related to the HPA axis being much more sensitive to environmental stimuli in *Lurcher* mutants compared to wild type mice (Frederic *et al.* 1997; Hilber *et al.* 2004). Chronically increased levels of ACTH and CORT inhibit follicle development, luteinizing hormone secretion and ovulation (Brann & Mahesh 1991). Therefore HPA axis hyper-reactivity may negatively influence oocyte development in *Lurcher* females.

In conclusion, *Lurcher* females showed reduced breeding capacity compared with healthy littermates. We hypothesize that, unlike other cerebellar mutants, anatomical disturbances of the reproductive system and motor impairment probably play a minor role in *Lurcher* mutant mice. Reduced numbers of offspring from *Lurcher* females is likely due to fewer pups being born and poor pup survival. Both these factors can be explained by HPA axis hyper-reactivity affecting oocyte development and triggering behavioral disinhibition caused by disruption of the central inhibitory system. The high incidence of maternal infanticide in *Lurchers* was probably a consequence of their behavioral disinhibition and abnormal stress reactivity, the pathogenesis of which involves the disappearance of cerebellar Purkinje cells. The hypothesis that HPA axis abnormalities and their secondary endocrine and behavioral consequences are probably responsible for the majority of reproduction disturbances in *Lurchers* is worth further examination using prenatal and behavioral studies.

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