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Original Article

Evaluation of Neonatal Sprague-Dawley Rats as a Potential Animal Model for the Neurovirulence Test of an Iranian Mumps Vaccine Strain, RS-12

Mohammad Kazem Shahkarami[1*], Mohammad Taqavian[1], Mohammad Hasan Hablolvarid[2], Ashraf Mohammadi[1], Abolhasan Foroughi[1], Reza Shahbazi[1], Mazyar ShahKarami[3], Ali Reza Yousefi[2]

1. Department of Human Viral Vaccines, Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran.
2. Department of Animal Pathology and Epidemiology, Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran.
3. Department of Industrial and Pharmaceutical Biotechnology, Faculty of Natural Sciences, Martin Luther University (MLU), Halle, Germany.

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ABSTRACT

Introduction: Mumps virus (MuV), a neurotropic member of paramyxoviridae, causes mumps disease. Since the 1960s, when the first live-attenuated vaccine against the MuV was developed, mumps outbreaks have dramatically decreased. A monkey-based neurovirulence test has been developed and has been used to assess the safety of attenuated MuV strains. However, laboratory and clinical findings have suggested that the monkey-based test may not necessarily reflect the neurovirulence behavior of the MuV when administered to the vaccinees. A neonatal rat-based MuV neurovirulence safety test has been developed and recommended by reference institutions in recent years. This test in Lewis rats was first introduced in 1998. This study aimed to evaluate the suitability of neonatal Sprague-Dawley rats for the neurovirulence test of an Iranian MuV vaccine strain, RS-12.

Materials & Methods: One-day-old Sprague-Dawley newborn rats were intracranially injected with MRC-5 cell supernatant (assigned as "C" for the control group), the RS-12 attenuated strain (assigned as "V" for the vaccine group), and the RS-12 wild-type strain (assigned as "W" for the wild-type group), respectively. The animals were observed for 30 days post-injection with regard to weight gain, viral titer in the brain tissue, and appearance of hydrocephalus in the brain sections.

*** Corresponding Author:**
Mohammad Kazem Shahkarami, Assistant Professor.
Address: *Department of Human Viral Vaccines, Razi Vaccine and Serum Research Institute, Agricultural Research, Education and Extension Organization (AREEO), Karaj, Iran.*
Tel: *+98 (26) 34050400* ***E-mail:*** *k.shahkarami@rvsri.ac.ir, shahkarami961@yahoo.com*

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Results: The mean weight gain in groups C and W was the highest and lowest respectively. Regression analysis of log-transformed weight values revealed a significant difference between group C and group W. A significant difference between group V and group W was seen. There was no significant difference between the weight gain of group C and group V. No MuVs were detected in the homogenized brain samples of group C, and in groups V and W, the viral titers showed a continuous decrease during the observation period. In the microscopic view of brain sections, the hydrocephalus started to form on day 15 post-injection and reached its highest extent on day 30. On day 30 post-injection, the hydrocephalus area was determined as a maximum of 1%, 5%, and 10% for the C, V, and W groups, respectively.

Conclusion: This study has introduced the newborn Sprague-Dawley rat model, capable of demonstrating the neurovirulence potential of MuV in vaccines and distinguishing between wild-type and attenuated RS-12 strains. Further experiments are needed for the optimization and validation of the test procedures.

1. Introduction

Mumps is a highly contagious, vaccine-preventable disease caused by a paramyxovirus [1]. The root of mumps is obscure, but it is probably associated with an Old English verb that means to grin, to grimace, or to mumble [2]. The mumps virus (MuV) circulates between humans by direct contact through respiratory droplets and contaminated fomites [1]. The disease occurs in 33% of unvaccinated people without clinical signs [3]. Non-specific symptoms such as anorexia, malaise, headache, and fever may occur, but the specific symptom is swelling of the parotid glands. Less common consequences are oophoritis, orchitis, mastitis, and pancreatitis. More serious consequences of infection are aseptic meningitis and encephalitis, which are considered rare complications [1]. In 40-50% of cases, particularly in children under five years old, mumps infection is associated with non-specific symptoms, especially respiratory signs. Mumps infection is not the only causative agent of parotitis [4, 5]. Immunity following natural mumps infection is generally long-lasting; however, re-infection may occur. In 75% of vaccinated individuals, mumps disease may occur without clinical signs [1].

1.1. Infectious agent

MuV has a non-segmented negative-sense RNA genome incorporated in an enveloped pleomorphic particle. MuV is classified in the genus *Orthorubulavirus* of the family Paramyxoviridae [1]. MuV has only one serotype, but based on the nucleotide sequence of Small Hydrophobic (*SH*) and haemagglutinin-neuraminidase (*HN*) genes, it is classified into 12 genotypes [6, 7]. The genome encodes seven proteins, including nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), SH, HN, and large (L) proteins [6]. Many cell types express MuV receptors, so the virus can enter a wide range of cells. However, Vero cells (African green monkey kidney cells) are widely used for virus isolation and propagation in laboratories [2]. Although humans are the only natural hosts of MuV, various species such as monkeys, hamsters, mice, rats, and chicken embryos are susceptible to MuV infection [2]. A newborn-rat model has been investigated for MuV neurovirulence over the past two decades, demonstrating potential for use in preclinical neurotoxicology testing (for example, in the assessment of vaccine safety) and in studies of the molecular basis of viral neurovirulence [2, 8].

1.2. Mumps vaccine history

In 1934, a virus was identified as the etiological agent of mumps. MuV was first cultivated in chicken embryos by Habel and Enders in 1945. As a result of successful cultivation of MuV in chicken embryos and cell cultures, an inactivated vaccine was developed in 1946 and tested in humans in 1951. However, it is no longer administered due to the short duration of immunity following vaccination. The first live attenuated mumps vaccine was developed in the United States in the 1960s [9]. Since then, global administration of live attenuated mumps vaccines has resulted in effective disease control and a dramatic decrease in outbreaks [8]. However, inadequate cross-protection among MuV strains —particularly when the vaccine strain doesn't match the genotype of circulating MuV —may contribute to the failure of global mumps elimination efforts [8].

1.3. Neurovirulence of MuV and the safety of mumps vaccines

As a neurotropic and neurovirulent virus, MuV is capable of infecting the central nervous system in a proportion of mumps cases [8]. All currently in-use mumps

vaccines contain live-attenuated viruses [2], so it is essential to ensure the safety of mumps vaccines [8]. Mumps vaccine strains such as Jeryl Lynn, Leningrad-3, L-Zagreb, Urabe, and others have been developed and certified for vaccine production during the last decades [9]. Although it is rare, it has been reported that some vaccine strains, such as Leningrad and Urabe, may be capable of shedding from vaccinees and infecting unvaccinated or vaccinated individuals [10, 11]. Therefore, to evaluate the neurovirulence and ensure the safety of mumps vaccines, neurovirulence tests should be carefully performed before starting clinical studies [8].

Mumps vaccines contain different live-attenuated strains, varying in immunogenicity, safety, efficacy, and adverse reaction profiles [12]. Several studies have been conducted to evaluate these characteristics [9, 13-16], providing the necessary information for national regulatory authorities to decide whether to manufacture and administer a mumps vaccine using a specific MuV strain or to reject it [17].

The most common animal model for studying the neurovirulence of MuV is rhesus monkeys. However, it is well-documented that mumps vaccines with acceptable safety profiles in monkey models may still cause meningitis and encephalitis in clinical use [8], and the neurovirulence test in a monkey model may not necessarily reflect the exact behavior of MuV in humans [18]. Moreover, many authoritative organizations have questioned the suitability of monkey models for the evaluation of MuV neurovirulence [8]. A neonatal rat-based MuV neurovirulence safety test has been developed and recommended by reference institutions in recent years. This model is much more convenient than monkey-based tests and can distinguish attenuated MuV strains from wild-type ones [8]. The neonatal rat-based MuV neurovirulence test in Lewis rats was first introduced by Rubin (1998) [8, 19] and gradually improved [20].

This study aimed to evaluate the suitability of neonatal Sprague-Dawley rats for the neurovirulence test of an Iranian MuV vaccine strain, RS-12. This was the first study on a neonatal rat-based MuV neurovirulence test in Iran.

2. Material and methods

2.1. MuV, RS-12 strain

Both wild-type and attenuated strains were provided by the Human Viral Vaccines Department, Razi Vaccine & Serum Research Institute. Historically, the virus was isolated from a clinically approved mumps patient. The wild-type virus was adapted to the human diploid cell line (MRC-5) following isolation and primary passages in Vero cells. The virus was attenuated using serial passages in MRC-5 cells [21].

2.2. Newborn rats

Sprague-Dawley newborn rats were provided by the Animal Husbandry Department, Razi Vaccine & Serum Research Institute.

2.3. Cell substrates

MRC-5 and Vero cells were provided by the Human Viral Vaccines Department, Razi Vaccine & Serum Research Institute.

2.4. Group assignments

Three groups of animals were assigned as C, V, and W. Group C (control) contained 3 mothers and 26 newborn rats (C1-C3). Group V (vaccine strain-injected) contained 3 mothers and 37 neonatal rats (V1-V3). Group W (wild-type-virus injected) contained 3 mothers and 34 neonatal rats (W1-W3). Each mother, along with her newborn rats, was kept in a dedicated cage.

2.5. Injection materials

One-day-old newborn rats in group C, group V, and group W were injected with 20 microliters of MRC-5 cell supernatant, 20 microliters of the RS-12 attenuated (vaccine) strain sample containing 103.5 viruses per mL, and 20 microliters RS-12 wild-type strain sample containing 103.5 viruses per mL, respectively.

2.6. Injection method

Sterile Hamilton syringes were used. The neonatal rats were gently fixed and subjected to intracranial injection in the left hemisphere, 2-3 mm in depth, at a location between the lambda and bregma regions. The injections were carried out under mild anesthesia.

2.7. Observation and sampling

The animals were observed for 30 days post-injection. All animals were weighed daily at 11:00 AM, including the day before injection. Any unusual observations, including deaths, were recorded. On days 3, 6, 9, 12, 15, 19, 25, and 30 post-injection, an animal from each group was selected randomly. Following a deep anesthesia, the brains were carefully removed, and a sagit-

Table 1. Viral titer in the homogenized brain tissues

Day Post-injection	Mean of Viral Titer in the Homogenized Brain Samples (-log CCID50/mL)							
	3	6	9	12	15	19	25	30
Group C	ND	ND	ND	ND	ND	ND	ND	ND
Group V	3.25	3.17	3.00	3.08	3.00	2.75	2.50	ND
Group W	3.5	3.45	3.42	3.75	3.75	3.13	ND	ND

Abbreviations: C: Control; V: Vaccine-injected group; W: Wild-type-injected group; ND: Not detected.

Note: Titer of MuV during the 30-day observation period. Mean values from three titrations are reported as final titers.

tal cut was made at the midline. The right hemispheres were homogenized in 1.5 mL DMEM (cell culture medium), and after centrifugation, the supernatants were frozen at -40 ˚C for further virus titration. The left hemispheres were fixed in formaldehyde solution for further pathological evaluation.

2.8. Virus titration

The titer of MuV in the homogenized brain samples was determined using the Kurbur formula.

2.9. Pathological evaluation

Formalin-fixed, paraffin-embedded blocks were sectioned and stained using the Hematoxylin-Eosin (H&E) staining method. The sections were microscopically observed for any pathological signs, particularly the formation and the extent of hydrocephalus in the lateral ventricle.

3. Results

The weight gain pattern, appearance of hydrocephalus in the lateral ventricles, and viral titer in the homogenized brain samples were followed as the main criteria of the neurovirulence test in a newborn rat-based model, according to the references.

The mean of weight gain in the C, V, and W groups showed a continuous increase during the 30-day observation period. The mean weight gain in groups C and W was the highest and lowest, respectively. Unlike group C, where weight gain continued to increase until the end of observation period, groups V and W entered a stationary phase on day 28 post-injection (Figure 1). Regression analysis of Log-transformed weight values revealed a significant difference between group C and group W. There was also a significant difference between group V and group W. However, no significant difference was observed between group C and group V.

The titer of MuV in homogenized brain samples is summarized in Table 1. Each sample was tested three times, and the mean of calculated titers was considered as the viral titer. No MuV was detected in the samples of group C. In groups V and W, the viral titers showed a continuous decrease throughout the observation period.

Sagittal sections were evaluated for the appearance of pathological signs, particularly hydrocephalus in the lateral ventricle. Hydrocephalus started to form on day 15 post-injection and reached its highest extent on day 30. To quantify the extent of hydrocephalus, the area of the formed cavity in the lateral ventricle was compared against the whole brain section, excluding the conus and the optic lobe. By day 30 post-injection, the hydrocephalus area reached a maximum of 1%, 5%, and 10% in the C, V, and W groups, respectively (Figures 2 and 3).

4. Discussion

Considering the neurotropic nature of MuV, the safety requirements of mumps vaccines should be carefully met by the manufacturers [22]. One of the most important safety aspects of the mumps vaccine is the neurovirulence potential of the MuV vaccine strain in humans [19]. These concerns have emerged following reports of neurovirulence-related symptoms in some vaccine recipients [19]. The risk of developing new live-attenuated mumps vaccines using strains with neurovirulence potential may persist unless an animal model becomes available with the ability to distinguish neurovirulent from non-neurovirulent strains [19].

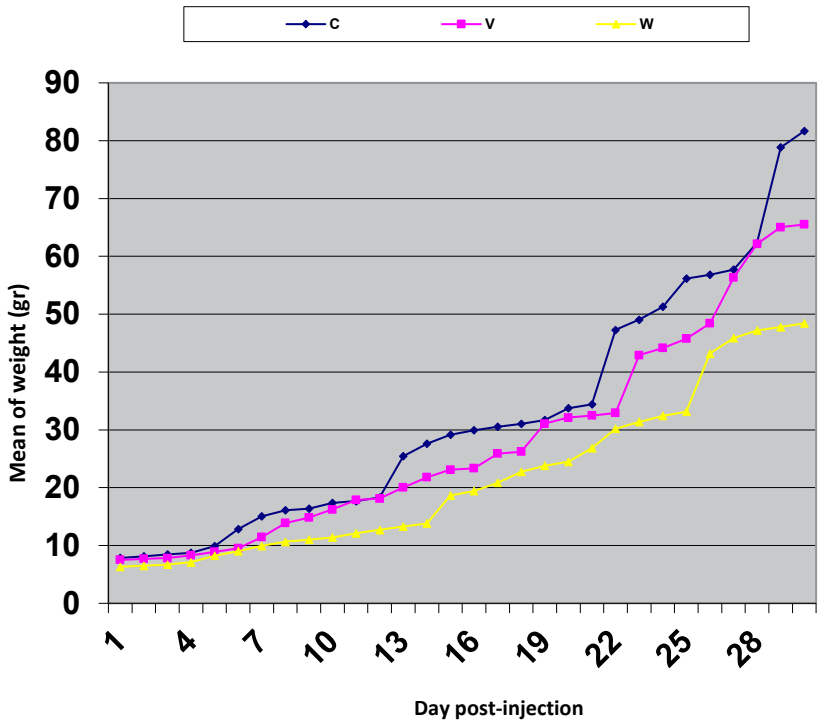

Figure 1. Mean weight gain of injected animals

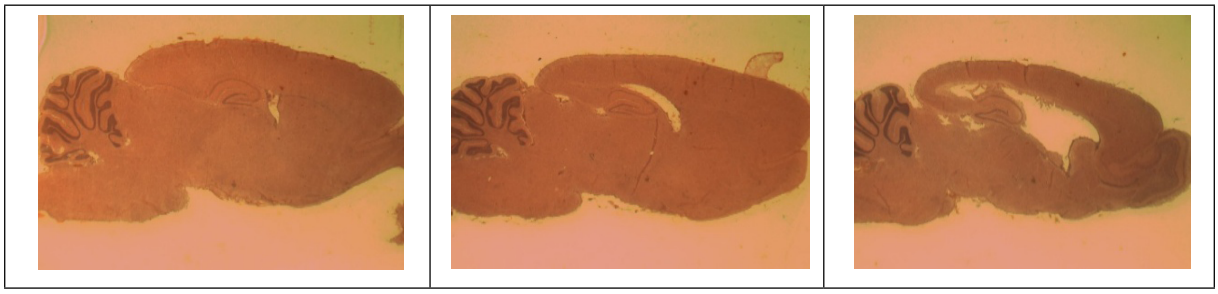

Figure 2. Microscopic view of sagittal brain sections on day 25 post-injection

A) Control group (injected with supernatant of MRC-5 cells); B) Group V (injected with attenuated RS-12 MuV); C) Group W (injected with wild-type RS-12 MuV).

Note: Formation of hydrocephalus is visible as hollow areas in the sections.

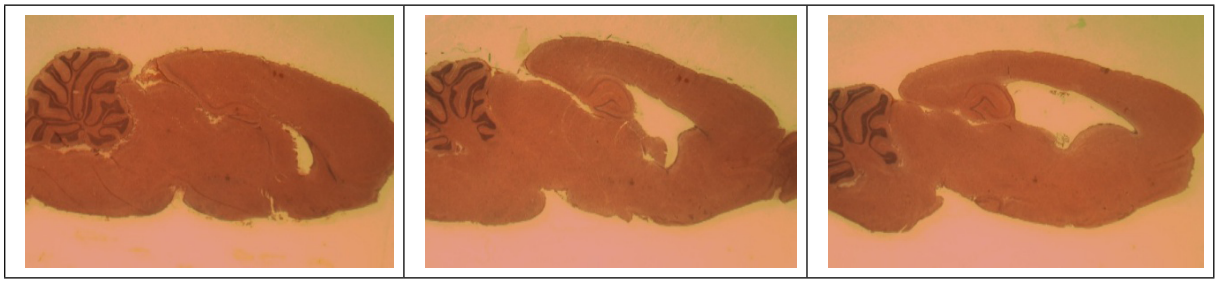

Figure 3. Microscopic view of sagittal brain sections on day 30 post-injection

A) Control group (injected with supernatant of MRC-5 cells); B) Group V (injected with attenuated RS-12 MuV); C) Group W (injected with wild-type RS-12 MuV)

Note: Formation of hydrocephalus is visible as hollow areas in the sections.

Currently, the standard method for assessing the neurovirulence risk of human vaccines, as recommended by the World Health Organization (WHO), is to test the vaccine's seed stocks in monkey models [19, 20, 22]. However, the neurovirulence test of the mumps vaccine strains in monkeys (MNVT) is questionable in terms of the reliability of its results [22], since the test is not sufficiently robust to predict the neurovirulence phenotype of MuV strains in humans [23]. The clinical and pathological consequences of a vaccine strain of the MuV in monkeys do not necessarily reflect the neurovirulence of that strain in vaccinees [19]. In other words, the MNVT test is not a true and accurate representation of the risk of neurovirulence in humans. According to reports, the MNVT also cannot distinguish between wild-type and attenuated MuVs that are isolated from CSF in post-vaccination aseptic meningitis cases [22]. There have been attempts to improve the efficacy of MNVT for the accurate prediction of MuV neurovirulence in humans [23]. It is therefore necessary to develop alternative animal models for evaluating the neurovirulence of MuV [22].

Attempts to introduce a murine model for MuV neurovirulence have been unsuccessful [22]. However, hamsters, as small animal models that are widely used in pathology studies [19], have not been capable of reliably distinguishing neurovirulent strains from non-neurovirulent ones [8, 18]. Moreover, studies on targeted mutagenesis with the aim of developing non-neurovirulent MuV strains have faced difficulties in the evaluation of efficacy due to the lack of a suitable animal model. Introducing an animal model that reliably predicts MuV neurovirulence in humans could also dramatically help to define the relationship between molecular markers of MuV neurovirulence with greater certainty [19].

Successful attempts have been made over the years to introduce newborn rats as a reliable animal model of MuV neurovirulence [5, 19, 20, 22, 23]. The early stages of these studies were conducted with an emphasis on the qualitative aspect, such that a highly neurovirulent strain called Kilham and a very harmless vaccine strain called Jeryl-Lynn were injected into the brains of newborn rats, and three important factors —including the weight gain pattern, the viral titer in the brain tissue, and pathological signs in the brain sections —were considered as indicators of neurovirulence assessment [19]. The results of this study showed differences in the process of weight gain, the incidence of hydrocephalus, as well as the ability to recover the virus from the animal's brain [19]. As the next step, more strains of MuV were included in the test, and a scoring system for the severity of hydrocephalus was established in the test hereafter called RNVT [23]. Subsequent studies have also demonstrated the validation and reproducibility of the RNVT, and its accurate prediction of the neurovirulence pattern of different strains of MuV (including wild, partially attenuated, or fully attenuated). Software has also been used to calculate the RNVT score [20].

The main aim of this study was to evaluate the neurovirulence of wild-type and vaccine strains of an Iranian MuV, RS-12, in a newborn rat model. In the literature review, it was found that all RNVT tests were performed on Lewis rats. Since the Lewis strain was not available, it was decided to conduct this experiment using Sprague-Dawley newborn rats. This study was designed and conducted with a qualitative view to understand whether the evaluation of neurovirulence criteria (weight gain pattern, formation of hydrocephalus, and recovery of MuV from the brain samples) following injection of RS-12 into Sprague-Dawley newborn rats is possible. Neither Sprague-Dawley newborn rats nor the RS-12 MuV strain had been examined in an RNVT before, so no data on the amount and viral titer suitable for injection into the brain were available. However, according to the methodology of a similar study [22], the volume of injection material per animal was adjusted to 20 microliters of viral samples containing 103.5 particles/mL. The control group was injected with the same volume of MRC-5 cell supernatant, the same cell line that had been used in the propagation of the RS-12 strain.

The weight gain curve of the C, V, and W groups showed the same pattern until day 5 post-injection but started to differ thereafter. Group C and group W experienced the lowest and highest weight gains, respectively. The difference between the weight gain of group V (which had been injected with the attenuated RS-12) and group W (which had been injected with wild-type RS-12) was statistically significant. It means that, regarding weight gain, Sprague-Dawley newborn rats can distinguish between wild-type and attenuated RS-12 viruses. These observations are fully consistent with the data reported in the corresponding articles.

Signs of hydrocephalus first appeared on day 15 post-injection and reached the highest degree on day 30, when hydrocephalus was measured at 1%, 5%, and 10% in the C, V, and W groups, respectively. In the relevant articles, signs of hydrocephalus were observed on day 12 post-injection. This three-day delay may be related to the nature of the viral strain and the strain of animal used. In the first RNVT study [19], there was also a report of signs of damage to the cerebellum on day 19 post-injection. Although in this study some abnormalities in

the cerebellum's texture were seen in W and V groups on day 25 post-injection, we did not pay more attention to the cerebellum, since it has been ignored in more recent studies. Based on the suggested scoring system, 0%, up to 6%, up to 12%, and up to 26% hydrocephalus are considered as negative, mild, moderate, and severe, respectively [23]. Therefore, the grade of hydrocephalus in this study could be reported as mild for group V and moderate for group W. Regarding this finding, newborn Sprague-Dawley rats seem to be capable of distinguishing between wild-type and attenuated RS-12 strains. The pathogenesis of hydrocephalus caused by MuV is not well understood. However, it is proposed that the severity of hydrocephalus correlates with the ability of different strains of MuV to replicate in the rats' brain [23].

The mean of viral titer in the group W brain samples decreased until day nine post-injection, then it increased and reached its maximum on day 15 post-injection, followed by a decrease such that the virus was not detected after day 19 post-injection. In the case of group V, the decrease in viral titer continued until day 25, when the virus became undetectable thereafter. These findings are consistent with similar studies [20, 24]. However, there are slight differences that may be related to the differences between Lewis and Sprague-Dawley rats and the viral strain in use (RS-12). In addition, it should be noted that RS-12 wild-type and attenuated strains had been included in the current study, whereas a completely safe vaccine strain (Jeryl Lynn) was compared against a highly neurovirulent strain (Kilham) in the referenced study. Since the severity of the neurovirulence of wild RS-12 has not yet been compared with a highly neurovirulent strain such as Kilham, it cannot be expected to achieve the same results. However, isolating the virus from the brain preparations (which represents the replication of the virus in the animal's brain) and obtaining similar results in terms of the coincidence of the decrease in viral titer and the development of neuropathological symptoms are very valuable and promising. Moreover, the fact that the attenuated virus was isolated from the brain for a longer period compared to the wild-type one may be attributed to the lower severity of brain damage in the animals injected with the attenuated virus.

5. Conclusion

This study has introduced a newborn Sprague-Dawley rat model capable of demonstrating the neurovirulence potential of MuVs in humans and distinguishing between wild-type and attenuated RS-12 strains. Further experiments are needed for the optimization and validation of the test procedures.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Razi Vaccine & Serum Research Institute, Karaj, Iran [Code: Nº 2-18-18-89038].

Data availability

All data analyzed during this study are included in this article.

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Authors' contributions

Conceptualization, study design, data analysis and interpretation: Mohammad Kazem Shahkarami and Mohammad Taqavian; Data acquisition: Mohammad Kazem Shahkarami, Mohammad Taqavian, Ashraf Mohammadi, Mohammad Hasan Hablolvarid, and Mazar ShahKarami; Statistical analysis: Ali Reza Yousefi; Material support: Reza Shahbazi, Abolhasan Foroughi; Supervision and writing: Mohammad Kazem Shahkarami.

Conflict of interest

The authors declared no conflict of interest.

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