

Review Article

Floppy Rabbit Syndrome in Pet Rabbits: A Differential Diagnostic Framework in Light of Recent Clinicopathological Evidence

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Floppy rabbit syndrome (FRS) has long been regarded as an idiopathic, peracute neurological condition of pet rabbits, with the published record consisting mainly of client-facing case narratives, brief conference proceedings, and passing textbook mentions rather than systematic clinicopathological investigation. A retrospective study published in 2026, building on an antecedent single-institution thesis dataset, provided the first substantive clinicopathological evidence on the condition: affected rabbits show a peracute, symmetric, lower-motor-neuron tetraparesis with markedly elevated serum creatine kinase (and, in the antecedent dataset, aspartate aminotransferase) that normalizes alongside clinical recovery, while hypocalcemia, hypokalemia, and infection with *Encephalitozoon cuniculi* or *Toxoplasma gondii* were specifically tested for and found unlikely to explain the syndrome. This narrative review situates that evidence within the broader differential landscape of acute generalized weakness in rabbits, synthesizing the best-supported differential categories — *E. cuniculi* infection, hypocalcemia/hypokalemia and dietary imbalance, toxicosis (particularly lead), and spinal or traumatic causes — into a single practical diagnostic framework that reflects which of these have already been tested against FRS specifically and which remain reasonable extrapolations. Two etiologies occasionally cited in secondary and tertiary sources, listeriosis and mesenteric vascular events, are examined and found to lack adequate species-specific evidentiary support for the acute flaccid tetraparesis phenotype characteristic of FRS, and are therefore excluded from the proposed framework pending further evidence.

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1. Introduction

Floppy rabbit syndrome (FRS) describes a peracute onset of generalized muscle weakness in pet rabbits, typically presenting as a symmetric, flaccid tetraparesis with reduced spinal reflexes and preserved mentation, appetite, and autonomic function. Affected rabbits are frequently found unable to rise, hop, or support their own weight, yet remain alert and willing to eat when food is placed within reach. The majority of cases resolve with supportive care alone within a few days, though the course and completeness of recovery vary.

Despite decades of clinical recognition among rabbit practitioners, FRS lacked a dedicated, peer-reviewed clinicopathological investigation until recently; the sparse case-level and conference-proceeding reports that did exist relied on small, uncontrolled observations rather than systematic data collection. This scarcity of primary data left clinicians without a validated framework for distinguishing FRS from its mimics, and left the syndrome's own pathophysiology essentially unexamined.

This gap changed in 2026 with the publication of the first retrospective clinicopathological study of FRS. The present article does not attempt an exhaustive systematic review — the underlying primary literature remains too sparse for that — but instead offers a narrative synthesis: it integrates the new clinicopathological findings with the best-supported differential categories drawn from the wider rabbit medicine literature, and proposes a practical diagnostic sequence for the practitioner confronted with an acutely weak rabbit.

Search strategy

PubMed-indexed records and general web-based search engines were searched from database inception through August 2026 using combinations of the terms “floppy rabbit syndrome”, “rabbit”, “*Oryctolagus cuniculus*”, “tetraparesis”, “acute weakness”, “*Encephalitozoon cuniculi*”, “hypocalcemia”, “hypokalemia”, and “lead toxicosis”, in English. Reference lists of retrieved articles were hand-searched for additional relevant sources. Given the sparse and heterogeneous nature of the primary literature on FRS specifically — consisting largely of case-level and conference-proceeding reports prior to 2026 — a formal systematic review with quantitative synthesis was not feasible; the search instead informed a structured narrative synthesis, with each source assessed individually below for study design, sample size, and the strength of the rabbit-specific (as opposed to extrapolated or cross-species) evidence it provides.

2. The 2026 Clinicopathological Study: A Turning Point

Polovitzer-Warum et al.^[1] conducted the first peer-reviewed retrospective study to systematically characterize FRS using clinical and clinicopathological data, building on and expanding an earlier, unpublished institutional case series from the same research group covering 2010–2022^[2]. Rabbits were included on the basis of a peracute, progressive, symmetric lower-motor-neuron tetraparesis, defined by generalized weakness in all four limbs together with decreased muscle tone and diminished spinal reflexes. Among the nine rabbits meeting these criteria in the published study, all were otherwise clinically unremarkable — feeding, urination, and defecation were preserved throughout — and all showed significantly elevated serum creatine kinase (CK) concentrations; the earlier institutional series additionally reported concurrent elevation of aspartate aminotransferase (AST) where measured^[2]. Eight of the nine rabbits recovered fully within a short period, and in the antecedent series recovery of motor function was observed to track closely with normalization of CK activity^[2].

Beyond establishing a clinicopathological marker, this research programme has already tested, and found wanting, two of the differentials most often repeated in the secondary literature. In the antecedent institutional series, hypokalemia and hypocalcemia were specifically investigated and could be excluded as causes of FRS in the rabbits studied, and infectious agents — specifically *E. cuniculi* and *Toxoplasma gondii* — were considered very unlikely to play a causal role^[2]. Only the markedly elevated AST and CK activities were felt to point toward a possible associated myopathy, though no definitive underlying cause was identified. The authors additionally drew an explicit analogy to Guillain-Barré syndrome in humans and idiopathic polyradiculoneuritis in dogs — both acute, largely self-limiting lower-motor-neuron or peripheral nerve disorders of suspected immune-mediated origin — as plausible comparative models for FRS, though this remains a conceptual analogy rather than a confirmed mechanism^[2].

This body of work is clinically useful for several reasons. First, it provides the first objective clinicopathological marker reported in association with FRS, moving the syndrome beyond a purely exclusionary, history-and-examination-based diagnosis. Second, it directly tests — rather than merely repeats — several long-assumed differentials, and finds two of them (electrolyte derangement and the two infectious agents tested) poorly supported as causes of this specific presentation. Third, the tracking of clinical recovery with CK normalization, together with the explicit comparison to immune-mediated peripheral neuropathies in other species, points toward a working hypothesis of FRS as a self-limiting myopathic or lower-motor-unit process of still-undetermined, possibly immune-mediated, origin.

Important limitations remain. The published cohort is small ($n = 9$, with an antecedent single-institution series of $n = 8$ covering a narrower window), muscle biopsy and electromyography were not performed, and a definitive unifying cause has not been established in either dataset. Consistent with the principle that findings from a small, single-institution series should not be generalized beyond their context, the exclusion of hypocalcemia, hypokalemia, and the two infectious agents tested should be read as applying to the specific cohort studied rather than as a categorical closure of these differentials for every rabbit presenting with acute weakness; a clinician encountering an individual case should still confirm rather than assume normal calcium, potassium, and infectious status, both because case-level exceptions are possible and because these conditions remain relevant differentials in their own right even where they do not explain FRS itself.

3. Differential Diagnostic Framework

Acute generalized weakness in a pet rabbit is not a single-disease presentation, and FRS should be regarded as a diagnosis of exclusion until the pattern of history, examination, and basic diagnostics has ruled out its principal mimics. The four categories below were retained from a broader review of conditions reported to cause acute or peracute generalized weakness in rabbits, on the criterion that at least one rabbit-specific primary or secondary source directly linking the condition to a weakness presentation could be identified; candidate categories for which no such rabbit-specific support could be found are addressed separately in Section 3.5 rather than silently omitted. This is not a claim that the four retained categories are exhaustive, and clinicians should continue to exercise judgment for presentations that do not fit any of them cleanly. A summary comparison is provided in Table 1.

3.1. *Encephalitozoon cuniculi* Infection

Encephalitozoon cuniculi is a widely prevalent microsporidial parasite of domestic rabbits, capable of producing granulomatous meningoencephalitis, nephritis, and phacoclastic uveitis^[3]. Central nervous system involvement most classically produces vestibular signs — head tilt, nystagmus, ataxia, and rolling — though paresis and generalized weakness have also been reported^[3]. Serology (IgM/IgG) can support antemortem suspicion, though a positive titer reflects exposure rather than confirmed active disease, and seroprevalence in pet rabbit populations is high enough that a positive result alone cannot establish causation in a given case of weakness^[3]. Notably, the antecedent institutional case series underlying the 2026 study specifically investigated *E. cuniculi* (together with *Toxoplasma gondii*) in its

FRS cohort and considered infection with either organism very unlikely to be causally responsible for the syndrome^[2]. This is a useful corrective to secondary sources that list *E. cuniculi* as a leading explanation for FRS-like presentations by default. It does not, however, remove *E. cuniculi* from the differential list for acute rabbit weakness in general: a clinician should still weigh serology and the classically asymmetric, vestibular-dominant presentation of encephalitozoonosis against the symmetric, non-vestibular pattern more typical of FRS, particularly in cases that deviate from the classic FRS picture.

3.2. *Hypocalcemia, Hypokalemia, and Dietary Calcium–Phosphorus Imbalance*

Rabbits possess a calcium metabolism that is unusual among mammals: rather than tightly regulating serum calcium through variable intestinal absorption, rabbits absorb dietary calcium in near-direct proportion to intake and excrete the surplus renally, so that serum calcium concentrations track dietary calcium more closely than in most other domestic species^[4]. A diet deficient in calcium relative to phosphorus can precipitate secondary hyperparathyroidism and, in more severe derangements, clinically relevant hypocalcemia^[4]. Calcium and potassium are each essential to normal neuromuscular excitability, and on general physiological grounds both hypocalcemia and hypokalemia are plausible causes of acute generalized weakness in mammals broadly. However, the antecedent institutional series underlying the 2026 study specifically tested for, and was able to exclude, both hypokalemia and hypocalcemia as causes of FRS in the rabbits studied^[2]. As with the infectious differentials in Section 3.1, this finding should be read as applying to FRS specifically rather than as evidence that electrolyte derangement cannot cause weakness in rabbits by other mechanisms; basic serum calcium, phosphorus, and potassium measurement remains inexpensive, low-risk, and a sensible early step in any rabbit presenting with acute weakness, both to catch the case that does not fit the FRS pattern and to document, rather than assume, a normal result before attributing the presentation to FRS.

3.3. *Toxicosis*

Clinical toxicoses are an uncommon but well-documented cause of neurological and systemic signs in pet rabbits, most often arising from environmental lead exposure — for example, gnawing on lead-based paint in older housing — as well as from certain rodenticides, household chemicals, and ingested plants^[5]. Lead toxicosis in rabbits has been repeatedly documented in the case-report literature, with presentations ranging from nonspecific lethargy and gastrointestinal hypomotility to, less commonly, neurological signs such as tremor and ataxia^{[6][7]}. A thorough environmental history — recent access to

paint, batteries, treated wood, or unfamiliar plants — together with basic hematology (screening for basophilic stippling or other lead-associated red cell changes) and, where indicated, blood lead concentration, allows this category to be reasonably excluded or confirmed without extensive additional testing.

3.4. Spinal and Traumatic Causes

Vertebral fracture or luxation, most often affecting the thoracolumbar or lumbosacral spine, is a well-recognized cause of acute hindlimb or generalized weakness in rabbits, frequently the result of a fall, an inappropriately restrained struggle, or a witnessed or unwitnessed traumatic event. Unlike FRS, spinal trauma classically produces asymmetric or regionally localized deficits, may be accompanied by pain on spinal palpation, and can usually be identified or excluded through orthogonal radiography of the spine. Given the potentially poor prognosis and specific management implications of a traumatic spinal lesion compared with the generally self-limiting course of FRS, radiographic exclusion of vertebral injury is an appropriate early step in the diagnostic sequence, particularly when a history of a fall or acute traumatic event is present or cannot be excluded.

3.5. Categories Excluded from the Core Framework: Listeriosis and Mesenteric Vascular Events

Some secondary and tertiary sources on FRS list listeriosis and acute splanchnic or mesenteric vascular events among the differentials for acute generalized weakness. On examination of the primary literature, neither is well supported as a cause of the specific flaccid, symmetric tetraparesis phenotype characteristic of FRS. Listeriosis in rabbits is most classically a septicemic or reproductive disease of late-pregnancy does, presenting with lethargy, inappetence, and abortion rather than a peracute generalized motor syndrome in otherwise healthy animals; antemortem diagnosis is rare precisely because the disease does not typically present with this pattern. Acute mesenteric or splanchnic vascular events, meanwhile, are described in the human medical literature as causes of abdominal pain and systemic illness, but no rabbit-specific evidence was identified linking such an event to generalized flaccid paralysis. Both categories are therefore omitted from the core diagnostic framework proposed here; clinicians who encounter case-specific evidence supporting either should of course weigh that evidence, but neither should be treated as a routine differential for FRS on current evidence.

A summary comparison of the core differential framework is provided in Table 1 (submitted as a separate file).

4. Proposed Diagnostic Sequence

Building on the differential categories above and the clinicopathological marker identified by Polovitzer-Warum et al.^[1], the following practical sequence is proposed for the rabbit presenting with acute generalized weakness:

1. History and signalment — onset speed, recent trauma or fall, diet composition and recent changes, environmental access to paint, chemicals, or unfamiliar plants, reproductive status and stage if female.
2. Neurological examination — confirm symmetric, generalized lower-motor-neuron pattern (decreased tone and reflexes in all four limbs) as opposed to asymmetric, vestibular, or spinally localized signs.
3. Orthogonal spinal radiography — to exclude vertebral fracture or luxation, particularly where trauma is reported or cannot be excluded.
4. Basic biochemistry — total or ionized calcium, phosphorus, and potassium, and serum creatine kinase (and AST where available); hematology to screen for lead-associated red cell changes where environmental exposure is plausible. Note that electrolyte derangement was specifically tested for and excluded as a cause of FRS in the foundational cohort (Section 3.2), but should still be documented rather than assumed in each new case.
5. *E. cuniculi* serology — as a supporting, not confirmatory, test; the foundational cohort found infection with *E. cuniculi* or *T. gondii* unlikely to explain FRS specifically, but serology remains a reasonable check, particularly for atypical or asymmetric presentations (Section 3.1).
6. Supportive care and reassessment — in the absence of a specific diagnosis and given the generally favorable short-term prognosis reported for FRS, supportive care (assisted feeding, thermal support, monitoring of urination and defecation) with structured reassessment over the following days is a reasonable default, with the working diagnosis of FRS supported retrospectively by spontaneous improvement.

5. Clinical Take-Home Points

- FRS is a diagnosis of exclusion, not a default explanation for acute rabbit weakness.
- A symmetric, generalized, lower-motor-neuron pattern with preserved mentation and appetite favors FRS over its principal mimics.
- Elevated serum creatine kinase (and, where measured, AST), while based on a small evidence base, is a useful supporting finding, tracks with clinical recovery, and should be checked routinely.
- Hypocalcemia, hypokalemia, and infection with *E. cuniculi* or *T. gondii* have specifically been tested for and found unlikely to explain FRS in the foundational cohort — but should still be documented, not assumed, in each new case.
- Spinal radiography, basic calcium/phosphorus/potassium biochemistry, and a toxin-focused environmental history allow rapid, low-cost exclusion of the best-supported differentials.
- The overall prognosis for FRS, once its mimics are reasonably excluded, is good, with most rabbits recovering fully within days on supportive care alone, and recovery tracks with normalization of CK.

6. Limitations

This article is a narrative synthesis rather than a systematic review, reflecting the genuinely limited primary literature currently available on FRS; as described in the Search Strategy above, the sparseness and heterogeneity of this literature made a quantitative systematic synthesis impractical. The foundational clinicopathological work on which much of this framework rests spans a published cohort ($n = 9$) and an antecedent, unpublished single-institution thesis dataset ($n = 8$) from the same research group, neither including muscle biopsy or electromyographic confirmation of the underlying lesion, and both should be regarded as hypothesis-generating rather than definitive. The exclusion of hypocalcemia, hypokalemia, and *E. cuniculi*/*T. gondii* infection as causes of FRS (Sections 3.1–3.2) is drawn from this same small, single-institution body of work and has not yet been independently replicated elsewhere; the possibility that a different population of FRS-like cases could implicate one of these factors cannot be excluded. The toxicosis and spinal-trauma categories (Sections 3.3–3.4), by contrast, are supported by an independent, more extensive case-report literature not specific to FRS — a difference in evidentiary base across categories that readers should weigh when applying this framework. The relative frequency of each differential category as a cause of an FRS-like presentation remains unknown, and the Guillain-Barré/idiopathic polyradiculoneuritis analogy discussed in Section 2 is, at present, a conceptual

comparison rather than a demonstrated shared mechanism. Prospective, multi-institutional studies incorporating standardized diagnostic testing, and where possible muscle biopsy, electrodiagnostic evaluation, or immune-mediated disease markers, are needed to establish whether FRS represents a single underlying entity or a shared clinical endpoint of several distinct, still poorly characterized processes.

7. Conclusion

Floppy rabbit syndrome has moved, for the first time, from an entirely anecdotal entity to one supported by systematic clinicopathological data, including a direct test — rather than a repetition — of several long-assumed differentials. This shift creates an opportunity, and a need, to consolidate the syndrome's differential diagnosis into a coherent, evidence-weighted framework rather than the loosely inherited lists that have circulated in the secondary literature to date, and to take seriously the emerging hypothesis of FRS as a self-limiting, possibly immune-mediated lower-motor-unit process analogous to Guillain-Barré syndrome and canine idiopathic polyradiculoneuritis. The framework proposed here, limited to categories with adequate species-specific support and explicit about where that support is only partial or drawn from a single research group, is intended as a practical starting point for clinicians and as a foundation that subsequent, larger, multi-institutional studies can refine, replicate, or revise.

Statements and Declarations

Funding

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Potential Competing Interests

No potential competing interests to declare.

Ethics

This article is a literature-based narrative review. It did not involve the collection of new data from human participants or live animal subjects, and no primary research involving animals was conducted by the author. Accordingly, no ethical approval or institutional review was required for this work.

Data Availability

No new data were generated for this review; all sources are cited in the reference list.

Use of Generative AI

An AI-assisted research tool was used to support literature searches and verify bibliographic information. All information provided by the AI tool was independently reviewed by the author. The selection and accuracy of sources, as well as all scientific content, interpretations, evaluations, and conclusions presented in this work, remain the sole responsibility of the author.

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