

1 **Sporadic acute benign calf**
2 **myositis: systematic literature**
3 **review**

4
5 **Running head:** Sporadic acute benign calf myositis
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25 **Word counts: SEZIONNE CHE DEVE METTERE A POSTO SEBA**

26 **Abstract:** 196 words

27 **Body of the manuscript:** 2037 words

28 **References:** 76

29 **Tables:** 3

30 **Figure:** 1 (black and white)
31
32

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38 Abstract

39 Acute benign calf myositis is a rare infection-associated syndrome
40 presenting with calves' pain. It occurs in epidemics or
41 sporadically. ~~In order to better characterize the sporadic form~~
42 ~~and increase the awareness of this condition,~~ we reviewed the
43 literature reporting apparently sporadic cases. The National
44 Library of Medicine was searched using the terms 'myalgia cruris'
45 OR 'benign childhood myositis' OR 'acute calf myositis' OR 'viral
46 myositis'. We identified ~~72 70~~ reports, including ~~447 451~~
47 patients, ~~322 325~~ males and ~~126 125~~ females. Sporadic acute benign
48 calf myositis affected subjects ≤ 18 years of age (N=~~446 450~~; 99%),
49 followed a prodromal flu-like illness (N=~~405 411~~; 91%), presented
50 with pain and tenderness affecting uniquely the calves for $\leq 1\frac{1}{2}$
51 weeks (N=~~441~~; 99%) and was never complicated by acute kidney
52 injury. The creatine kinase level was elevated in ~~441~~ (99%) out of
53 ~~444~~ cases. Microbiological studies identified an infectious
54 trigger in ~~177 181~~ cases, mostly Influenzavirus (type B more
55 frequently than type A), Dengue, Epstein-Barr or Parainfluenza
56 virus and Mycoplasma pneumoniae.

57 Sporadic acute benign calf myositis is a self-limited condition
58 that can usually be diagnosed on a clinical basis. Differently
59 from the epidemic form, many cases are due to microorganisms other
60 than Influenzavirus B or A.

61

62 **Keywords:** Acute benign myalgia cruris • Acute toe walking • Benign
63 childhood myositis • Bottom shuffling • Frankenstein walk • Review

64 1. Introduction

65 First described 60 years ago by the Swedish pediatrician Åke
66 Lundberg as myalgia cruris, acute benign calf myositis is a
67 peculiar infection-associated syndrome of muscle pain [1]. It
68 presents with pain and tenderness affecting the calves, habitually
69 recovers within a week and can occur in epidemics or sporadically.

70 Epidemic cases are usually associated with Influenzavirus of
71 type B [2]. Sporadic cases, however, might be associated with a
72 large number of microorganisms. Furthermore, during an outbreak
73 there is a great alertness that promotes earlier diagnosis. **There**
74 **is likely a lower awareness regarding the sporadic form,**
75 **compromising an early and correct diagnosis and giving potentially**
76 **rise to unneeded ancillary investigations. In order to**
77 **characterize the sporadic form of acute calf myositis and increase**
78 **the knowledge of this condition, we** systematically reviewed the
79 literature reporting sporadic cases of acute calf myositis.

80

81 2. Methods

82 2.1. Literature search strategy

83 Between September 2016 and **June 2017**, we performed a computer-
84 based search with no date or age limits of the terms 'myalgia
85 cruris' OR 'benign childhood myositis' OR 'acute calf myositis' OR
86 'viral myositis' in the National Library of Medicine database.
87 Personal files and the bibliography of each identified report were
88 also screened. We **applied** the principles underlying the U.K.
89 Economic and Social Research Council guidance on the conduct of

90 narrative synthesis and the 'Preferred reporting items for
91 systematic reviews and meta-analyses' statement.

92 **2.2. Selection criteria**

93 Reports published in Dutch, English, French, German, Italian,
94 Portuguese or Spanish were included. When more than one article
95 reported on the same patient, only the more comprehensive one was
96 retained. For the final analysis, we included apparently
97 previously healthy subjects of both ~~sexes~~ genders and all ages
98 presenting with acute onset pain and tenderness principally
99 affecting the calves, normal sensor examination, preserved ankle
100 and knee reflexes, and spontaneous remission [2]. An elevated
101 total creatine kinase level was not a prerequisite for diagnosis.
102 The following cases were excluded: patients with acute benign calf
103 myositis developing in the context of an outbreak of ≥ 10 cases and
104 occurring during one season in a defined geographical area [1, 2],
105 cases developing in individuals managed with potentially myotoxic
106 drugs and cases possibly triggered by intense exercise or a sudden
107 increase in exercise in an untrained person ≤ 3 days before leg
108 pain onset. In order to ascertain the eligibility, authors of
109 reports were sometimes requested for additional information.

110 ~~The prodrome was considered typical if characterized by a flu-~~
111 ~~like illness (fever, malaise, nasal discharge or cough) lasting ≤ 2~~
112 ~~weeks and atypical if characterized by a flu-like prodrome lasting~~
113 ~~> 2 weeks, by non flu-like symptoms and signs (e.g. diarrhea) or in~~
114 ~~cases without prodrome. The presentation was considered typical in~~
115 ~~cases with bilateral calf symptoms lasting $\leq 1\frac{1}{2}$ weeks and atypical~~
116 ~~in cases with symptoms lasting $> 1\frac{1}{2}$ weeks, in cases with unilateral~~

117 ~~calf symptoms or in cases with calf pain associated with~~
118 ~~widespread muscle aches.~~

119 **2.3 Data extraction**

120 From each report, data on gender and age; general past history;
121 prodrome; duration of calf pain; general and neurologic
122 examination with emphasis on calf pains and gait abnormalities;
123 highest enzyme levels; tests to identify an underlying infection;
124 management; electromyography or muscle biopsy; and complications
125 such as leukopenia ($<4.5 \times 10^9/L$), thrombocytopenia ($<150 \times 10^9/L$),
126 acute kidney injury, cardiac or cerebral involvement and
127 recurrences were excerpted [2] using a structured schedule
128 established in advance. The literature search and the data
129 extraction were carried out by two investigators independently.
130 Disagreements were resolved by discussion until consensus.

131 **2.4 Analysis**

132 To pool the data of different studies, weighted central values
133 were calculated using equations that assign weight in proportion
134 to the size of the sample. In publications without statistical
135 dispersion data such as standard deviation, range or interquartile
136 range, the weighted dispersion was taken from the remaining
137 reports. Continuous data are presented as median and interquartile
138 range, dichotomous data as relative frequency and percentage. The
139 Cohen's index was used to assess the agreement between
140 investigators on the application of the inclusion and exclusion
141 criteria, the Fisher's exact test to compare dichotomous variables
142 and the Mann-Whitney-Wilcoxon test to compare continuous
143 variables. Statistical significance was assigned at $P < 0.05$.

144 3. Results

145 3.1. Search Results

146 The literature search process is summarized in figure 1. The
147 chance-adjusted agreement between the two investigators on the
148 application of the inclusion and exclusion criteria was 0.91. For
149 the final analysis, we retained ~~70~~ 72 scientific reports [~~3-72~~ 3-
150 ~~74~~] published between 1973 and 2017: ~~26~~ 28 from Europe, 19 from
151 Asia, 15 from North America, 6 from South America and 4 from
152 Oceania. They were published in English (N=~~54~~ 55), Spanish (N=10),
153 French (N=2), German (N=2), ~~Dutch~~ (N=1), Italian (N=1) and
154 Portuguese (N=1). The communications included a total of ~~447~~ 451
155 previously healthy subjects affected with apparently sporadic
156 acute calf myositis.

157 3.2. Findings

158 3.2.1. Prodrome - presentation

159 Age, gender, clinical features, laboratory findings and disease
160 course of the ~~447~~ 451 patients appear in table 1. ~~Calf myositis~~
161 ~~was preceded by a flu-like illness in >90% and presented with~~
162 ~~bilateral calf pain in 95% of cases. Muscle aches lasted $\leq 1\frac{1}{2}$ weeks~~
163 ~~in 99% of cases. The typical prodrome, detected in 405 (91%) of~~
164 ~~cases was characterized by a flu-like illness (fever, malaise,~~
165 ~~nasal discharge or cough) lasting ≤ 2 weeks. A flu-like prodrome~~
166 ~~lasting >2 weeks (N=2), a diarrheal prodrome (N=4) or no prodrome~~
167 ~~(N=36) were observed in the remaining 42 (9%) cases. 419 (94%)~~
168 ~~patients showed a typical presentation and course, characterized~~
169 ~~by bilateral calf symptoms lasting $\leq 1\frac{1}{2}$ weeks. In further 28 (6%)~~

170 ~~patients, presentation was atypical. It was characterized by~~
171 ~~isolated unilateral calf pain (N=4), calf pain accompanied by~~
172 ~~thigh pain (N=12; bilateral in 10 and unilateral in 2), severe~~
173 ~~bilateral calf pain associated with mild widespread muscle aches~~
174 ~~(N=8) or muscle symptoms lasting >1½ weeks (N=4). Three-hundred-~~
175 ~~eighty-six (86%) patients characteristically presented with a flu-~~
176 ~~like prodrome and bilateral calf pain lasting ≤1½ weeks.~~
177 ~~Complexively, prodrome (N=37), presentation (N=23) or both~~
178 ~~prodrome and presentation (N=5) were atypical in 65 (15%) and~~
179 ~~typical in the remaining 382 (85%) cases. Age (7.0 [5.4-9.1]~~
180 ~~versus 7.2 [4.9-9.8] years) and gender (~~278~~ 283 ♂ and ~~102~~ 103 ♀~~
181 ~~versus 42 ♂ and 23 ♀) were not statistically different in cases~~
182 ~~with typical prodrome and presentation characteristic features as~~
183 ~~compared with the remaining 65 (14%) cases. Sporadic acute calf~~
184 ~~myositis was preceded by a typical flu-like illness in 405 (91%)~~
185 ~~cases. A flu-like prodrome lasting >2 weeks (N=2), a diarrheal~~
186 ~~prodrome (N=4) or no prodrome (N=36) were observed in the~~
187 ~~remaining 42 (9%) cases. Presentation and course were typical in~~
188 ~~419 (94%) and atypical in 28 (6%) cases: isolated unilateral calf~~
189 ~~pain (N=4), calf pain accompanied by thigh pain (N=12; bilateral~~
190 ~~in 10 and unilateral in 2), severe bilateral calf pain associated~~
191 ~~with mild widespread muscle aches (N=8) and muscle symptoms~~
192 ~~lasting >1½ weeks (N=4).~~

193 Calf aches were reported to be associated with gait
194 abnormalities in at least ~~356~~ 358 cases (table 2). A skin rash was
195 observed in 16 (4%) cases (including a petechial rash in 7 cases

196 affected with dengue and the characteristic slapped cheek and lacy
197 rash in 2 cases of erythema infectiosum due to Parvovirus B19).

198 The total creatine kinase level, determined in 444 cases, was
199 found to be elevated in 441 (99%) cases. The total creatine kinase
200 ratio, calculated by dividing the measured level by the
201 corresponding upper limit of normal, was ≥ 100 in 6 (<2%) cases.
202 Elevated aminotransferases were also reported in 57 patients (the
203 elevation of aspartate aminotransferase was more pronounced than
204 that of alanine aminotransferase in these cases). The total
205 creatine kinase to cardiac MB isoenzyme ratio, a myocardial injury
206 marker, was measured in 33 (7%) cases and found to be always
207 normal.

208 **3.2.1. Microbiological studies**

209 Microbiological studies were performed in ~~260~~ 264 (~~58~~ 59%)
210 cases. A possible infectious trigger was identified in ~~177~~ 181 (~~68~~
211 69%), as given in table 3. Influenzavirus (type B more frequently
212 than type A), Dengue virus, Epstein-Barr virus, Parainfluenza
213 virus and Mycoplasma pneumoniae were the most commonly identified
214 microorganisms. Cases associated with Influenza or Parainfluenza
215 virus and cases associated with other microorganisms did not
216 differ with respect to clinical features, creatine kinase test and
217 time to recovery.

218 **3.2.2. Special investigations**

219 Electromyography, performed in 21 (5%) cases, disclosed a
220 characteristic myopathic pattern in 11 cases (52%) but was normal
221 in the remaining 10 cases (48%). A needle biopsy of the soleus
222 muscle, performed in 8 (2%) cases, revealed mild infiltration of

223 polymorphonuclear or mononuclear white blood cells, muscle
224 necrosis and muscle fiber regeneration. Search for bacterial or
225 viral genome was never performed.

226 **3.2.3. Management - complications - recurrences**

227 The patients were managed symptomatically and supportively.
228 Macrolides were prescribed in the 7 cases associated with a
229 mycoplasma infection. Antiviral agents such as oseltamivir were
230 never prescribed.

231 The total blood cell count (table 1) disclosed mild leukopenia
232 or thrombocytopenia in approximately two-thirds (62%) and one
233 fourth (22%) of cases, respectively. Acute kidney injury and
234 cardiac or cerebral involvement were never reported. Recurrences
235 were observed in 13 cases (3%): one recurrence in 11 and two in 2
236 cases.

237

238 **4. Discussion**

239 This review of the literature reveals that sporadic acute benign
240 calf myositis, like epidemic benign calf myositis [2],
241 characteristically follows a prodromal flu-like illness and
242 affects preschool- and school-aged children with a male-to-female
243 ratio of approximately 2:1. It presents with pain, tenderness, and
244 occasionally swelling affecting the calves, gait abnormalities,
245 normal sensor examination, preserved tendon reflexes and elevated
246 total creatine kinase level, is never complicated by myositis-
247 associated acute kidney injury, mostly recovers within 4 days and
248 recurs in <5% of cases. Furthermore, sporadic acute benign calf

249 myositis is often associated with mild leukopenia,
250 thrombocytopenia or both (a common finding in a large number of
251 viral infections) and is not associated with nervous system and
252 cardiac involvement. Unlike epidemic cases, which are almost
253 always due to Influenzavirus of type B or A [2], approximately
254 half of the reported sporadic cases are temporally associated with
255 further microorganisms such as Epstein-Barr virus,
256 Parainfluenzavirus, Mycoplasma pneumoniae and especially Dengue
257 virus [75]. Finally, calf myositis is sometimes preceded by a skin
258 rash or an infectious diarrheal disease.

259 Muscle biopsy studies, performed in a minority of sporadic cases
260 presenting with a flu-like prodrome and bilateral calf pain, point
261 out that acute benign calf myositis is an inflammatory muscle
262 disease. Investigations in epidemic influenzavirus B-associated
263 cases support the notion that in this condition muscle damage
264 results from a direct viral invasion [2]. More studies are needed
265 for further elucidating the mechanisms underlying this condition.

266 In the vast majority of cases, sporadic acute benign calf
267 myositis is a stereotyped clinical condition (acute onset of
268 bilateral calves' pain following an acute flu-like illness, normal
269 sensor examination with preserved ankle and knee reflexes), whose
270 diagnosis can be presumed with an excellent degree of confidence
271 based on history, physical examination and creatine kinase
272 determination alone and subsequently confirmed based on the
273 clinical course (spontaneous remission within 1½ weeks). Further
274 evaluation [2, 57] might be recommended exclusively in subjects
275 living in tropical and subtropical areas (or with history of

276 recent travel to the mentioned areas), with muscle symptoms not
277 preceded by a flu-like illness, with unilateral calf pain or calf
278 swelling, with calf pain associated with widespread muscle aches,
279 with abnormal neurological examination or with muscle symptoms
280 lasting >1½ weeks. The differential diagnosis includes arthritis,
281 cerebellar ataxia, dermatomyositis, fractures, Guillain-Barré
282 syndrome, osteomyelitis,
283 thrombosis, transverse myelitis and vasculitides such as
284 periarteritis nodosa or isolated calf muscle vasculitis [2, 76].

285 Finally, inherited diseases impairing the muscular energy
286 production should be considered following two or more attacks [2].

287 The total creatine kinase level is substantially elevated in
288 inflammatory muscle diseases including calf myositis. The activity
289 of the creatine kinase cardiac MB isoenzyme, a marker of cardiac
290 injury, was determined in a minority of patients affected by
291 sporadic acute calf myositis and found to be normal. Since this
292 test is occasionally pathologically altered in inflammatory
293 myositis or after marathon running even in the absence of a
294 myocardial damage, a sensitive troponin test is advised if to
295 exclude a myocardial compromise. Electromyography, although
296 integral in the evaluation of a suspected chronic myopathy, can
297 notoriously be normal in a number of myopathies. No distinctive
298 myopathic abnormalities were disclosed in many patients with
299 sporadic acute calf myositis, confirming the assumption that a
300 normal electromyography does not exclude the presence of a
301 myopathy [76]. Finally, we suppose that, in some patients,

302 electromyography was performed relatively late in the course of
303 this brief-lasting disease.

304 The course of both sporadic and epidemic [2] acute benign calf
305 myositis is never complicated by acute kidney injury. Hence, we
306 recommend testing for kidney function only in cases with
307 generalized muscle pain, red to brown urine and creatinine kinase
308 values ≥ 100 times normal. This assumption is supported by
309 observations in adults pointing out that a kidney injury occurs
310 almost exclusively if the creatinine kinase is $\geq 40,000$ UI/L on
311 admission [77].

312 Sporadic acute calf myositis usually (75%) recovers within 4
313 days. This is why we advise for characteristic cases no more than
314 adequate hydration, administration of analgesics if needed and
315 sometimes bed rest.

316 The results of this review must be viewed with an understanding
317 of the inherent limitations of the analysis process, which is
318 based on the scanty available literature. Two limitations of this
319 work should be specifically stated. First, available data do not
320 allow documenting the prevalence of sporadic acute benign calf
321 myositis. Second, since microbiologically uncharacterized cases
322 are less likely to be published than cases caused by Dengue virus,
323 our data might overestimate the frequency of this microorganism as
324 a cause of acute calf myositis. Third, the reported recurrence
325 rate is likely rather inaccurate because it depends on the length
326 of follow up.

327

328 5. Conclusions

329 Many cases of sporadic acute benign calf myositis are due to
330 microorganisms other than Influenzavirus B or A. Like epidemic
331 benign calf myositis [2], sporadic acute benign calf myositis is a
332 self-limited condition that can generally be easily diagnosed on a
333 clinical basis. In characteristic cases, ancillary investigations
334 such as electromyography and muscle biopsy are unwarranted. The
335 information generated from this review will help physicians to
336 become more familiar with ~~it~~ this benign condition.

337 **Funding**

338 - Ettore Balli Foundation, Bellinzona, Switzerland.

339 - Dr. Sebastiano A. G. Lava is recipient of research grants from
340 the Fondazione Ettore e Valeria Rossi and from the Swiss National
341 Science Foundation.

342

343 **Competing interest**

344 The authors declare no conflicts of interest.

345

346 **Ethical approval**

347 Not applicable / not required (Review of the literature).

348

349 **Authors' contribution**

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352 - Acquisition, analysis, and interpretation of data: Gioele
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359

360 **Acknowledgments**

361 - The authors would like to thank Dr. Alec Villa for his
362 assistance in the linguistic revision.

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551

552 **Figure 1 - Legend**

553 Sporadic acute benign calf myositis. Flowchart of the literature
554 search process. * We unsuccessfully contacted the authors of the
555 study to ascertain eligibility.