Risk of Leukemia in Children With Peripheral Facial Palsy

Franz E. Babl, MD*; Amit Kochar, MD; Michael Osborn, MBBS; Meredith L. Borland, MBBS; Adam West, MBBS; Amanda Williams, RN; Stuart R. Dalziel, PhD; on behalf of the PREDICT network

*Corresponding Author. E-mail: franz.babl@rch.org.au.

Most children with peripheral facial palsy will not have a cause identified. Although leukemia can cause facial nerve palsy, the magnitude of the risk is unknown and recommendations for investigations are variable. We are currently conducting a randomized, placebo-controlled trial of prednisolone for the treatment of Bell's palsy in children within the Paediatric Research in Emergency Departments International Collaborative emergency research network. In the course of the assessment for eligibility of the trial, from 644 acute-onset facial palsy presentations we identified 5 children with previously undiagnosed leukemia. We estimate the rate of leukemia in children with acute-onset facial palsy who present to emergency departments to be 0.6% (95% confidence interval 0.2% to 1.6%). In accordance with these cases, we suggest consideration of a screening CBC count for acute-onset peripheral facial palsy presentations in children before initiation of corticosteroid treatment. [Ann Emerg Med. 2021;77:174-177.]

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INTRODUCTION

Bell's palsy, or acute idiopathic peripheral facial paralysis, is characterized by sudden-onset unilateral paralysis or weakness of the muscles of the face controlled by the facial nerve. The incidence of Bell's palsy in the United States is 18.8 per 100,000 per person-year.[1] Although the cause of Bell's palsy is unknown, the diagnosis requires exclusion of other causes of facial palsy, including infectious, traumatic, inflammatory, cerebrovascular, and neoplastic conditions.[2-4] Usually the diagnosis is clinical.[4-7] Data on what proportion of isolated peripheral facial palsy in children is due to Bell's palsy are variable and depend on the referral bias.[8,9]

Although corticosteroids have been shown to improve the rate of complete recovery in adults with Bell's palsy,[10,11] similar high-level placebo-controlled evidence regarding corticosteroid use is not available for children.[12,13] We are currently conducting a triple-blinded, randomized, placebo-controlled trial of prednisolone for the treatment of Bell's palsy in children (Bell's Palsy in Children trial) at 11 emergency departments (EDs) in Australia and New Zealand.[12] During the trial period, we have so far encountered 5 cases of leukemia associated with peripheral facial palsy. In addition, we have noted the effect of corticosteroid treatment on the diagnosis and the therapeutic options in leukemia. Although we would normally report secondary findings such as the rate of leukemia at the end of the trial, we think that this information is of value now for clinicians to whom children with peripheral facial palsy present.

CASE REPORT

During 4 years, 153 patients with unilateral peripheral facial palsy were enrolled in the randomized placebo-controlled trial, with 1 case (case 1) of leukemia diagnosed (1/153, or 0.7%; 95% confidence interval 0.2% to 3.5%). Among the 644 patients ranging in age from 5 months to 17 years and presenting with acute-onset facial palsy who were screened for eligibility (including the enrolled patient), 5 patients had leukemia identified as the cause of the facial palsy, 4 without a history of leukemia (4/644, or 0.6%; 95% confidence interval 0.2% to 1.6%) (Table).

This study received ethics approved at The Royal Children's Hospital, Melbourne, Australia.

DISCUSSION

After the identification of leukemia in the first patient in this series, we investigated all patients with acute-onset facial palsy assessed for eligibility or missed in the randomized placebo-controlled trial at participating sites in terms of any subsequent changes in diagnosis to leukemia. We have identified a rate of leukemia of 0.6% in children presenting with acute-onset facial palsy in our prospective data collection to date. Previous case reports have described leukemia (both acute lymphoblastic leukemia and acute myeloid leukemia) as a cause of facial palsy.[14-16]

Table. Patients with facial palsy and leukemia.

Age, Years	Sex	History	Examination	RCT Enrollment	Course	Leukemia Diagnosis	Final Diagnosis
8	F	5 days of rectal pain and intermittent fever	Unilateral peripheral facial palsy	Included	Persistent palsy and new ipsilateral exophthalmos	CT with orbital infiltrates/CBC with pancytopenia and blasts	AML
7	M	3 days of facial weakness	Unilateral peripheral facial palsy and otitis media	Excluded	Presented with pneumonia and hypovolemic shock at day 6. Recurrence of facial palsy (6 wk).	CBC with elevated WBC count and blasts/ chest radiograph with mediastinal mass	T-cell ALL
5	F	1 day of facial weakness and ear pain	Unilateral peripheral facial palsy and otitis media	Excluded	Facial palsy resolved. Developed headaches and pallor (4 wk).	CBC with anemia, thrombocytopenia, elevated WBC count and blasts	pre-B ALL
9	F	5 days of facial weakness with fever and minor facial trauma	Unilateral peripheral facial palsy with blurred vision, ipsilateral eye swelling and tenderness over zygoma	Excluded		CBC count with anemia, thrombocytopenia, elevated WBC count and blasts	T-cell ALL
7	F	1 day of facial weakness with sore throat and ear pain. History of ALL in remission (5 y).	Unilateral peripheral facial palsy	Excluded		CBC with blasts/MRI with infiltrative changes of temporal bone and middle fossa	ALL (CNS relapse)

RCT, Randomized placebo-controlled trial; *F*, girl; *CT*, computed tomography; *AML*, acute myeloid leukemia; *M*, boy; *ALL*, acute lymphoblastic leukemia; *MRI*, magnetic resonance imaging; *CNS*, central nervous system.

However, it was unclear what the incidence of leukemia was in children with facial palsy who present to acute care de novo, nor was it clear how many patients who were treated with corticosteroids for presumed Bell's palsy subsequently received a diagnosis of leukemia. A 25-year single-center data set from Denmark reported 2 patients with leukemia in 180 pediatric patients with peripheral facial palsy outside the neonatal period, of whom 138 received a diagnosis of Bell's palsy.[9] No further details were reported. The study sites of the Bell's Palsy in Children randomized placebo-controlled trial are EDs at mainly tertiary care children's hospitals, which may have introduced bias.

In our setting, the diagnosis of Bell's palsy—facial palsy without other cause identified—is generally made clinically, with CBC count obtained for only 16% of patients in a retrospective chart review before the current randomized placebo-controlled trial.[7] According to our data, 161 patients (95% confidence interval 61 to 556) would need to be screened with a CBC count to identify 1 instance of leukemia if all new instances of leukemia could have been detected with a CBC count. Although the investigators of our trial had discussed the conduct of a CBC at the design stage, we opted not to include this investigation because it was not standard practice at participating Paediatric Research in Emergency Departments International Collaborative sites, which includes all tertiary care children's hospitals in Australia and New Zealand[17] and is not included in local clinical practice guidelines.[6] Recommendations for investigations are not addressed in the American Academy of Neurology guideline update on the use of corticosteroids and antivirals to treat Bell's palsy.[18] In 2013, the American Academy of Otolaryngology–Head and Neck Surgery Foundation published a clinical practice guideline that states that no laboratory testing or diagnostic imaging is recommended in the investigation of isolated facial nerve palsy except Lyme serology in endemic areas.[4] There is no Lyme disease in Australia and New Zealand. Investigations conducted in published case series are variable, with CBC count completed in up to 78% of cases in a small series from the United Kingdom.[19] Our series emphasizes that in patients with acute-onset peripheral facial palsy, specific causes of alternative systemic or ear-related diagnoses need to be carefully considered.

Corticosteroids induce apoptosis in lymphoblasts, and are a standard component of the treatment of acute lymphoblastic leukemia and most lymphoid malignancies. In the widely used Berlin-Frankfurt-Munster acute lymphoblastic leukemia protocols, a 1-week corticosteroid prephase (without any systemic chemotherapy) rapidly decreases the peripheral blood blast count to less than 1×10^9/L in greater than 90% of patients.[20,21] Consequently, the use of corticosteroids in children with occult leukemia may be problematic. It may delay the diagnosis of leukemia by improving the initial symptoms of peripheral facial palsy,[14] which likely happened in case 3. Acutely, the main concern is the precipitation of tumor lysis syndrome, a condition caused by the breakdown of malignant cells, which can lead to extensive metabolic derangement, potentially resulting in acute renal failure, cardiac arrhythmias, seizures, and death.[22] Presumably, this was the cause of the acute renal failure in case 2 after corticosteroid treatment, but was not appreciated at the time because the corticosteroids had cleared the circulating lymphoblasts.

Beyond the acute phase, acute lymphoblastic leukemia patients pretreated with corticosteroids are generally regarded as being at higher risk,[23] and may become ineligible for the cooperative group clinical trials that are standard of care in most pediatric oncology centers.[24,25] Patients with leukemia-related peripheral facial palsy are regarded as having central nervous system involvement, with resultant higher-intensity treatment regardless of findings on magnetic resonance imaging and cerebrospinal fluid cytology.[14]

In accordance with the leukemia cases identified and the severe consequences of diagnostic uncertainty, we have changed the Bell's Palsy in Children study protocol and are mandating the performance of a CBC count with differential as part of the screening process. Although the relative frequency of leukemia may be different in areas where Lyme disease is endemic, we believe a CBC count should be considered by the treating clinician in presentations of peripheral facial palsy, particularly when steroid therapy is planned.

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Author affiliations: From the Emergency Department, Royal Children's Hospital, and Murdoch Children's Research Institute, Parkville, Victoria, Australia (Babl, Williams); the Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Victoria, Australia (Babl); Paediatric Research in Emergency Departments International Collaborative (PREDICT), Melbourne (Babl, Kochar, Borland, West, Williams, Dalziel); Emergency Department, Women's and Children's Hospital, Adelaide, Australia (Kochar); the Department of Haematology and Oncology, Women's and Children's Hospital, North Adelaide, South Australia, Australia (Osborn); the Emergency Department, Perth Children's Hospital, and the Divisions of Emergency Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia (Borland); Monash Emergency Research

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