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Hydroxychloroquine as a steroid-sparing agent in an infant with chronic urticaria

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Hydroxychloroquine is an antimalarial drug frequently used to reduce inflammation in autoimmune and inflammatory conditions.^{1,2} In adults, hydroxychloroquine can be used as an alternative agent to treat antihistamine-refractory chronic spontaneous urticaria (CSU).³ It is unknown whether hydroxychloroquine is safe and effective for treating antihistamine-refractory CSU in children. We present the case of a 9-month-old male infant with 5 months of recurrent, unprovoked hives and swelling who was treated safely and successfully with hydroxychloroquine.

The patient was a previously healthy, full-term infant delivered by cesarean section. He was breastfed until 6 weeks of age and switched to a cow's milk-based formula without incident. After resolution of an upper respiratory tract infection at 4 months of age, he developed recurrent and unprovoked full-body hives. The hives were occasionally associated with angioedema of the hands and feet, would resolve within 24 hours, and were not associated with fevers, residual bruising, lymphadenopathy, or joint swelling. Review of systems was negative for constitutional, respiratory, cardiovascular, gastrointestinal, genitourinary, or neurologic symptoms. The hives did not improve with an empiric trial of hypoallergenic formula or elimination of solid foods. The hives were refractory to treatment with diphenhydramine, high-dose cetirizine, ranitidine, and montelukast. The hives resolved with systemic corticosteroids, but quickly recurred when corticosteroids were tapered. Physical examination showed a well-appearing infant with multiple annular urticarial lesions involving the face and body and mild angioedema of the hands and feet. A stroke test revealed marked dermatographism.

Notable laboratory studies at 6 months of age included platelets of 534,000/ μ L, C-reactive protein of 0.64 mg/dL (reference, <0.5 mg/dL), and erythrocyte sedimentation rate of 18 mm/h (reference, <15 mm/h). Total serum immunoglobulin E (IgE) and cow's milk-specific IgE were undetectable. Serum tryptase, complement C3 and C4 levels, and antinuclear antibodies were normal. Serologic studies for hepatitis B and C infection, Epstein-Barr virus heterophile antibodies, antineutrophil cytoplasmic antibodies, and rheumatoid factor were negative. Serum thyroid-stimulating hormone level was normal and serum antithyroid

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peroxidase and antithyroglobulin antibodies were undetectable. A 4-mm punch biopsy of a skin lesion showed mild superficial to deep perivascular lymphocytic and eosinophilic infiltrates without evidence of vasculitis.

At 9 months of age, the patient presented to our clinic requiring cetirizine (4 mg twice daily), ranitidine (37.5 mg twice daily), montelukast (4 mg/d), and prednisolone (0.65 mg/kg per day) to control urticaria. We initiated hydroxychloroquine at 2 mg/kg per day. Table 1 shows the time course of the patient's diagnostic workup, medication management, and symptom improvement. The patient developed diarrhea a few days after starting therapy. Hydroxychloroquine was reduced to 1 mg/kg per day and diarrhea quickly resolved. Hydroxychloroquine was increased to the target dose of 4 mg/kg per day over a 2-week period, without incident. Over 1 month, prednisolone was gradually weaned to 0.65 mg/kg every other day.

At 11 months of age, the patient had an acute recurrence of urticaria after receiving the inactivated influenza vaccine. Laboratory evaluation at that time was notable for persistent thrombocytosis, prompting referral to a hematologist for further evaluation. Peripheral blood smear analysis showed no evidence of blood dyscrasias. Additional diagnostic studies, including urinalysis, serum immunoglobulins, lactate dehydrogenase, and uric acid, were within normal limits. Ophthalmologic exam at 14 months of age was also normal. Control of urticaria was restored after increasing hydroxychloroquine to 6 mg/kg per day. Prednisolone was further tapered and completely discontinued by 15 months of age without recurrence of urticaria. Ranitidine and montelukast were discontinued at 16 months of age. At 17 months of age, hydroxychloroquine was decreased to 4 mg/kg per day. By 21 months of age, the patient had not experienced urticaria for nearly 9 months and hydroxychloroquine was tapered and discontinued by 24 months of age. The patient is currently healthy and free of urticaria at the time of this report.

Although children frequently experience episodes of acute urticaria, childhood CSU is considered rare.⁴ Childhood CSU is sometimes associated with infections, atopy, autoimmunity and physical urticarias, but most cases are idiopathic.⁵ Although large clinical studies are lacking, many children with recurrent urticaria appear to respond favorably to antihistamines.⁶ However, the optimal management of antihistamine-refractory CSU in children is unknown. This case demonstrates that low-dose hydroxychloroquine (4–6 mg/kg per day) is a safe and effective treatment option for infants with CSU requiring systemic corticosteroids for symptom control. Given the severe side effects associated with long-term corticosteroid therapy, deploying hydroxychloroquine as a possible steroid-sparing agent in infants with antihistamine-refractory CSU is highly appealing. Hydroxychloroquine may limit wheal formation by stabilizing lysosomes and inhibiting synthesis of cytokines and prostaglandins that promote vasodilation and increased vascular permeability involved in wheal formation.² Hydroxychloroquine has been used safely at up to 10 mg/kg per day to treat childhood autoimmune and inflammatory conditions, including systemic lupus erythematosus and surfactant protein C deficiency.^{1,7} Hydroxychloroquine is generally well tolerated, with gastrointestinal symptoms and macular rash the most common adverse effects. Ocular problems, including corneal deposits and irreversible retinopathy, are potentially serious side effects, although the risk of retinal damage is <1% when

hydroxychloroquine is used at low doses (5 mg/kg per day) for a duration of <5 years.^{8,9} Still, the American Academy of Ophthalmology recommends a baseline eye examination within 1 year of beginning treatment with hydroxychloroquine and annual screenings after 5 years of continuous use.⁹

Hydroxychloroquine offers several advantages over other immunomodulatory agents employed as second-line agents to treat chronic urticaria. An oral medication that can be administered at home, hydroxychloroquine does not require routine blood draws to monitor liver, kidney, or bone marrow function. It is possible that our patient's CSU resolved spontaneously rather than in response to hydroxychloroquine treatment. However, we believe this is unlikely given the severity of our patient's urticaria and need for combination therapy, which are risk factors for persistent disease.^{5,10} Furthermore, a recent study of children with CSU observed remission in only 10.6% and 44.5% of patients at 1 and 5 years, respectively.⁵ Although further study is needed, this case demonstrates that hydroxychloroquine can be a safe and potentially effective therapeutic option for antihistamine-refractory CSU in children, allowing for concomitant discontinuation of steroids.

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Table 1

Time Course of Diagnostic Workup, Medication Management, and Symptom Improvement

Age	Management	Symptoms
4–9 months	<ul style="list-style-type: none"> Intermittent week-long courses of prednisolone Daily high-dose H1 and H2 antihistamines, LTA 	Daily hives whenever prednisolone discontinued
9 months	<ul style="list-style-type: none"> Diagnostic tests as described in text High-dose H1 and H2 antihistamines, LTA, and prednisolone 0.65 mg/kg per day Hydroxychloroquine 2 mg/kg per day started Develops diarrhea Hydroxychloroquine dose decreased to 1 mg/kg per day and diarrhea resolves Hydroxychloroquine slowly increased to 4 mg/kg per day over 2 weeks 	Sporadic outbreaks of hives (approximately once every 2 weeks)
10 months	<ul style="list-style-type: none"> Prednisolone weaned to 0.65 mg/kg every other day 	Sporadic outbreak of hives (approximately once every 4 weeks)
11 months	<ul style="list-style-type: none"> Hives flare after influenza vaccine Hematology-oncology evaluation for persistent thrombocytosis and concern for malignancy Uric acid, vitamin B12, LDH, and total IgG, IgA, IgM, and IgE, all normal Hydroxychloroquine increased to 6 mg/kg/day Thrombocytosis resolves 	Sporadic outbreak of hives (approximately once every 4 weeks)
12 months	<ul style="list-style-type: none"> Dramatic clinical improvement No hives on hydroxychloroquine, prednisolone, LTA, and antihistamines Slow prednisolone taper started 	No hives
14 months	<ul style="list-style-type: none"> Routine ophthalmology evaluation—normal eye exam 	No hives
15 months	<ul style="list-style-type: none"> Prednisolone discontinued 	No hives
16 months	<ul style="list-style-type: none"> H2 antihistamine and LTA discontinued 	No hives
17 months	<ul style="list-style-type: none"> H1 antihistamine dose halved Hydroxychloroquine decreased to 4 mg/kg per day 	No hives
21 months	<ul style="list-style-type: none"> Hydroxychloroquine wean continued 	No hives
24 months	<ul style="list-style-type: none"> Hydroxychloroquine discontinued 	No hives

Abbreviations: IgA, IgE, IgG, IgM, immunoglobulin A, E, G, and M, respectively; LDH, lactate dehydrogenase; LTA, leukotriene antagonist.