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Methacholine Challenge in Children With Sickle Cell Disease: A Case Series

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Summary

Lung disease is a major cause of morbidity in children with sickle cell disease (SCD). Asthma in children with SCD is associated with a twice greater rate of pain and acute chest syndrome (ACS) episodes when compared to children with SCD but without asthma. Provocation challenges with methacholine are used to diagnose asthma when spirometry is normal, bronchodilator reactivity is absent, or the clinical picture is ambiguous. There have been only limited descriptions of use of methacholine challenge in individuals with SCD. We conducted a retrospective cohort study of 21 children with SCD and recurrent respiratory tract symptoms who were challenged with methacholine to determine if airway hyper responsiveness (AHR) was present. Fourteen (67%) of the children had a positive challenge. Of the 14 patients, four were given a new diagnosis of asthma based on the presence of chronic chest symptoms and the newly determined AHR and started on inhaled corticosteroids (ICS). In each positive challenge, forced expiratory volume in one second (FEV_1) was reversed to at least 90% of baseline 15 min after bronchodilator treatment. Oxygen saturation decreased in 93% of those with a positive challenge, but returned to baseline values 15 min after bronchodilator treatment. No patient developed a pain or ACS episode within at least 1 month after the challenge. Evaluation of AHR with methacholine challenge in patients with SCD appears to be well tolerated and may elucidate a cause of SCD morbidity.

Keywords

methacholine challenge; sickle cell disease; children; airway hyper responsiveness

INTRODUCTION

Among individuals with SCD, pulmonary complications contribute significantly to both morbidity and mortality.[1–3] When asthma is diagnosed in individuals with SCD, there is an associated increase in the incidence of pain and ACS episodes, and death.[4–6] Patients with SCD often have pulmonary symptoms that suggest the presence of asthma. Understanding

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whether these symptoms are due to asthma may be helpful in determining treatment. Detection of AHR by challenge testing is one such approach.

The presence of AHR in SCD has been studied primarily with cold air [7] and exercise [8,9] challenges. Both of these approaches have significant limitations in SCD. Cold air challenge may induce changes in lung function simply due to the induction of vasocclusion by cold temparature.[10,11] Application of an exercise stimulus can be limited due to deconditioning of children with severe chronic illness and the presence of chronic anemia with baseline hemoglobin levels commonly less than 8 g/dl.

Methacholine provocation challenge to evaluate AHR in patients with SCD has several advantages over cold air and exercise challenges. Methacholine challenges have an established safety profile in children and adults with asthma.[12,13] They can be done in individuals who can perform spirometry reproducibly without demands of conditioning or introduction of the concern that cold air may precipitate vasooclusion. Methacholine challenges have been used extensively in children and adults, both as a clinical test to confirm the diagnosis of asthma and as a research outcome measure to determine treatment efficacy. AHR determined by methacholine challenge is related to various measures of asthma severity [14] and has also been reported as a predictor of persistent asthma and airflow limitation in adulthood.[15] There have been only two reports of the use of methacholine challenge in SCD, one in 26 adults [16] and one in 31 children.[17] Neither publication reported significant adverse effects of the challenges.

While asthma among children with SCD is associated with an increased rate of pain and ACS,[4–6] making a diagnosis of asthma is often difficult in this population. This difficulty is due in part to the significant overlap between an ACS episode and an asthma exacerbation, as ACS is defined [3] as presence of a new radiodensity on chest radiograph, shortness of breadth and wheezing or cough, and a new requirement for supplemental oxygen, all of which occur commonly with an asthma exacerbation. Given the treatment implications of a diagnosis of asthma, our clinical approach has been to perform spirometry with assessment of a bronchodilator response. If bronchodilator responsiveness is absent but there is still a suspicion of asthma based on a clinical history, we perform a methacholine challenge to evaluate for AHR. In this case series, we report safety and clinical utility of children who had significant SCD morbidity, asthma suspected based on history of clinical symptoms, but had a negative bronchodilator response.

METHODS

Permission was obtained from the Washington University Human Research Protection Office to review medical records retrospectively without informed consent. Methacholine testing was carried out by trained and certified technicians in the clinical Pediatric Pulmonary Function Laboratory from 2/03 to 1/07. Physicians were available on-site to evaluate the child and initiate treatment as necessary. The procedure was performed at least 4 hr after the use of a short-acting bronchodilator and 24 hr after the last use of a long-acting bronchodilator or theophylline. The tests were not performed if any of the following conditions were present: an upper respiratory tract infection or use of oral corticosteroids within 4 weeks; presence of other serious illness; if the forced expiratory volume in one second (FEV_1) at baseline was <70% of predicted; the patient was pregnant.

The procedure was modified from the methods of Cockcroft et al.[18,19] and used by the Childhood Asthma Management Program.[20,21] Spirometry was performed following the ATS/ERS guidelines using a mass flow sensor (V_{max}, SensorMedics (Cardinal Health), Dublin, OH). At baseline, at least three acceptable Forced Vital Capacity (FVC) maneuvers

were performed, with at least 2 with values for FEV_1 and FVC repeatable within 5% or 200 ml. The flow-volume loops also met acceptable start and end of test criteria. The best curve for FEV_1 was selected for use in calculation of the concentration of methacholine that provides a 20% fall from baseline FEV_1 (PC_{20}). After the baseline measurements, the patient breathed a solution of normal saline using tidal breathing method with a Wright's nebulizer (Roxon Universal Medical, New West Minister, BC, Canada). The patient was seated comfortably with the facemask or mouthpiece and nose clips in place and then instructed to breathe normally for 2 min. Following the nebulization at least three acceptable FVC maneuvers were performed with at least 2 repeatable FEV_1 and FVC values. If spirometry results failed to meet acceptability or reproducibility, the testing did not proceed. Concentrations of methacholine were then delivered for 2 min using the same tidal volume inhalation from the Wright's nebulizer, starting with 0.195 mg/ml followed by doubling dilutions up to 12.5 mg/ml. At the end of each 2 min nebulization, the patient was questioned about the presence of symptoms with the possibility of stopping the testing if symptoms were severe, and spirometry was performed at 30 and 90 sec. A repeatable drop 20% or greater drop in FEV_1 was indicative of a positive challenge. Albuterol, 2 puffs using an aerochamber, was administered to relieve symptoms and hasten return of FEV_1 to baseline. The concentration that provoked a 20% fall from baseline FEV_1 was obtained by linear interpolation of the logarithmic dose–response curve expressed as PC_{20}. Oxygen saturation determined by pulse oximetry was monitored throughout the challenge procedure. A return of oxygen saturation to baseline levels was confirmed 15 min after the albuterol was administered.

RESULTS

Demographics

Methacholine challenges were performed on 21 children with SCD, 19 with HbSS or HbSBeta thalassemia zero (Table 1). Twenty of the 21 children had a history of an ACS episode. The child without a history of an episode of ACS (#18) had repeated sinusitis, exercise-induced shortness of breath, evidence of allergy to aeroallergens, and eczema. Eleven had been admitted to an ICU during a severe ACS episode, with seven requiring intubation (Table 1). Nine had at least one episode ACS in the prior 2 years, with a median of three episodes (range 1–7), relative to an anticipated rate of 0.8 episodes/year.[23] Seventeen had at least one pain episode[22] requiring hospitalization in the prior 2 years, with a median of three episodes (range 1–8), relative to an anticipated rate of 0.2 episodes/year.[22] None had a response to bronchodilator as defined by an increase of 12% or greater after administration of albuterol.[25] Spirometry results were consistent with obstruction in only one child (#10) (Table 2).

The reason for performing the methacholine challenges was to provide evidence for or against asthma in children with a negative bronchodilator response. Children had symptoms of cough, wheeze, or shortness of breath, but with normal spirometry or minimal obstruction defined by reference values from Wang et al.[24] All had been given albuterol for intermittent use with symptoms. Twelve of 21 had been given a provisional diagnosis of asthma and prescribed ICS for chronic use (Table 2). Nine had also been prescribed an asthma medication in addition to ICS (Table 2). Parental history of asthma was present in 24% (5 of 21) patients. Aeroallergen sensitivity was evident in 76% (13 of 17) for whom the skin prick testing was completed (Table 2). Lung volume testing using body plethysmography demonstrated air trapping (residual volume/total lung capacity >34% [26]) in 25% (4 of 16 tested) (Table 2).

Methacholine Challenge Testing was Well Tolerated in the Children With Sickle Cell Disease

Children were monitored in the pulmonary function laboratory until all symptoms had resolved, FEV_1 had returned to within 90% of baseline values, and oxygen saturation had returned to baseline values. Complete resolution of symptoms and a return to baseline values for FEV_1 and oxygen saturation occurred in all patients by 15 min following administration of albuterol after the PC_{20} had been achieved. The parents were instructed to call if the patient exhibited any new symptoms within the next 24 hr. No calls were received. No patient needed medication other than albuterol to relieve symptoms or return FEV_1 and oxygen saturation to baseline values, needed additional medical attention following the methacholine challenge, or had a temporally related pain or ACS episode. Children were followed in the St. Louis Children's Hospital SCD clinic for at least 8 months after the challenge procedure. The next admission to hospital for either pain or ACS occurred from 36 days to 2 years (median 3 months) after the methacholine challenge. Results of examination and symptoms reported by the patients during the challenge are presented in Table 3.

Oxygen saturation decreased during the challenge in 93% (13 of 14) when AHR was present, however, the decreases were not dependent on the degree of hyper responsiveness. Oxygen saturation values returned to baseline within 15 min of administration of albuterol in all patients with one exception. This was the only patient (#5) chronically on low flow nasal cannula oxygen. He did not achieve pre-challenge oxygen saturation on room air, but was fully oxygenated on his baseline 2 L of low-flow oxygen. None of the seven patients with a negative challenge had a change in oxygen saturation during the challenge.

Methacholine Challenge Testing Impacted Patient Management in Children With SCD

For the 14 children with positive challenges, ICS medications were continued in the 10 patients already receiving the drug and the importance of regular use was emphasized to the family using the result of the testing as evidence of importance. The four not receiving an inhaled anti-inflammatory medication were started on ICS. For the seven children with negative challenges, ICS was discontinued in one and reduced in dosage in another but not stopped because the parent felt that the medication had provided benefit. The other five patients with a negative challenge were not started on ICS.

DISCUSSION

Methacholine challenges were able to identify AHR in children with SCD where symptoms were suggestive of the asthma, but spirometry demonstrated a normal or a restricted pattern and there was no improvement in FEV_1 with bronchodilator administration. The test results helped clinicians to support use of ICS medication to the treat symptoms, most of which were chronic in nature and produced morbidity. Negative results allowed the clinicians to minimize additional medications and focus attention on disease processes other than asthma as a source of symptoms.

Ozbek et al.[17] also used methacholine challenge to detect AHR in children with sickle cell disease, 15 with HbSS and 16 with HbSβ, unselected for history of severe or frequent episodes of pain or ACS. They found 75% with positive challenges with an apparent increase in incidence of AHR in patients with a prior history of ACS. Adverse reactions to the methacholine challenges and levels of oxygen saturation during the challenges were not reported.

Of the patients with AHR in our series, the majority did have aeroallergen sensitivity suggesting that they may have typical asthma. However, SCD is a pro-inflammatory

state,[27–30] and while not specifically confirmed, this pro-inflammatory state may affect airways to induce AHR independent from the airway inflammation that occurs in asthma. Leong et al.[7] found AHR occurred in 64% of children with SCD who did not have symptoms consistent with reactive airway disease, suggesting that AHR could occur independently of asthma. A more complete understanding of the nature of AHR in patients with SCD needs to be obtained.

This study has some limitations. It is retrospective in a selected group of children with significant SCD-related morbidity. While the number of children is small, these children do represent those likely to be candidates for testing. The significant morbidity in these patients suggests that use of methacholine challenge testing can be safely performed in individuals with a past history of significant morbidity.

In conclusion, our experience with methacholine challenge testing supports the conclusion that this procedure can be performed safely and that it may provide useful clinical information.

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ABBREVIATIONS

SCD	sickle cell disease
ACS	acute chest syndrome
FEV_1	forced expiratory volume in 1 sec
PC_{20}	concentration of methacholine that provides a 20% fall from baseline FEV_1
AHR	airway hyper responsiveness
ICS	inhaled corticosteroids

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TABLE 1

Phenotype and History of Sickle Cell Disease Morbidity in the 21 Children

Patient	Age	Gender	Sickle cell phenotype	ACS episodes in past 2 years	Pain episodes in past 2 years	History of ICU admission
Patients with a positive challenge						
1	5.1	F	SS	1	0	Yes[1]
2	10.5	M	Sβthal+[1]	1	3	No
3	8.0	F	SS	2	4	No
4	15.1	F	SS	0	2	Yes[2]
5[3]	8.5	M	SS	NA[3]	NA[3]	Yes[1,2]
6	7.8	M	SS	0	0	Yes[1,2]
7	9.2	M	SS	0	1	No
8	18.7	M	SS	2	5	Yes[2]
9	12.3	M	SS	3	4	No
10	8.6	F	Sβthal0	2	4	No
11	14.0	M	SS	0	1	No
12	15.9	F	SS	0	6	Yes[2]
13	13.1	F	SS	0	8	Yes
14	17.1	F	SS	1	4	Yes[1]
Patients with a negative challenge						
15	13.5	M	SC	2	5	No
16	8.0	M	SS	0	1	Yes[1]
17	9.7	F	SS	0	1	Yes[1]
18[4]	8.8	F	SS	0[4]	0	No
19	13.4	F	SS	0	3	No
20	14.7	F	SS	0	1	No
21	7.6	M	SS	4	5	Yes[1,2]

[1] Patients with a history intubation during ICU admission.

[2] Patients with a history of exchange transfusion during ICU admission.

[3] This patient was referred from another center for evaluation that included the methacholine challenge and no hospital records were available.

[4] Only patient with no history of an ACS episode.

TABLE 2

Chronic Symptoms and Spirometry Results

Patient	Chronic symptoms[1]	FEV_1% predicted	FEV_1/FVC	% increase in FEV1 after bronchodilator	Medications used before challenge[2]	Parental history of asthma	Allergy to aeroallergens	TLC, % predicted	RV/TLC, %
Patients with a positive challenge									
1	1	78[3]	99	2%	ICS	No	No	NT	NT
2	1, 2, 3, 4	99	84	11%	ICS, LTRA	No	Yes	93	27
3	1, 3	91	95	NT[4]	None	Yes	Yes	NT	NT
4	1, 3, 4	82	82	4%	ICS, LABA	No	NT	97	23
5	1, 3	83	93	1%	ICS	No	Yes	84	34
6	1, 2, 4	94	93	NT	None	No	Yes	102	35[5]
7	1, 2, 3	94	83	6%	ICS, LABA	No	Yes	NT	NT
8	1, 2	88	78	4%	None	No	Yes	109	25
9	None	91	86	2%	ICS, LABA	Yes	Yes	92	30
10	1	64[3]	71[3]	9%	None	No	Yes	96	25
11	2, 3	115	87	1%	ICS, LABA	No	Yes	98	22
12	1, 3	77[3]	91	0%	ICS, LABA	No	NT	88	32
13	1, 3	106	84	1%	ICS, LABA	Yes	Yes	NT	NT
14	1, 2, 3, 4	96	87	2%	ICS, LABA	Yes	No	NT	NT
Patients with a negative challenge									
15	None	121	85	6%	None	No	Yes	113	34
16	None	83	91	5%	None	No	NT	112	19
17	1, 3	97	88	2%	None	No	NT	91	37[5]
18	3, 4	88	92	3%	None	Yes	Yes	100	35[5]
19	2, 3	85	97	2%	None	No	Yes	94	36[5]
20	1, 3, 4	88	83	–2%	ICS, LABA	No	No	89	33
21	1, 3	78[3]	91	2%	ICS	No	No	100	27

[1](1) Wheeze; (2) cough with exercise; (3) shortness of breath with exercise; (4) night time awakening from cough or wheeze.

[2] ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long acting bronchodilator agent.

[3] Below normal range (29).

[4] Not tested.

[5] Above normal range (24).

TABLE 3

Symptoms and 02 Saturations During Methacholine Challenges

Patient	PC_{20} (mg/ml)	Symptoms at PC_{20}[1]	O2 Saturations		
			Baseline	During challenge on room air	Recovery
Patients with a positive challenge					
1	0.784	1	98%	93%	97%
2	0.949	1, 2	100%	93%	>93%
3	2.22	1, 4	98%	95%	NR[2]
4	3.01	1, 2	99%	92%	98%
5	3.14	1, 4	99% on 2 L O_2/95% on room air	83%	89% on room air/99% on 2 L O_2
6	4.37	1	99%	95%	95%
7	4.41	None	93%	90%	NR[2]
8	4.44	None	92%	94%	94%
9	5.42	1, 2	93%	87%	93%
10	7.59	1, 3	99%	96%	99%
11	7.65	1, 2, 4	100%	93%	NR[2]
12	8.12	1, 3	91%	88%	94%
13	9.84	1, 2	100%	96%	NR[2]
14	9.86	1, 2, 4	93%	86%	NR[2]
Patients with a negative challenge					
15	Negative	None	98%	99%	99%
16	Negative	None	97%	96%	96%
17	Negative	None	100%	100%	100%
18	Negative	None	92%	92%	92%
19	Negative	None	91%	91%	91%
20	Negative	None	100%	100%	100%
21	Negative	None	100%	100%	100%

[1](1) Cough; (2) chest tightness or complaint of hard to breathe; (3) shortness of breath or difficulty breathing; (4) throat tight. Patients were routinely questioned at the time of reduction of FEV1 by at least 20% of the post-diluent value and the responses recorded in the record of the test.

[2] NR, not recorded in clinical record. Standard procedure in the clinical pulmonary function laboratory is to confirm return of a decreased oxygen saturation to baseline levels at the time of performing spirometry 15 min after administration of albuterol at time of determination of the PC_{20}. There were no comments in these cases of any abnormalities in oxygen saturation before discharge from the laboratory.